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ORIGINAL ARTICLES

THE ABSORPTION AND EXCRETION OF N-(PYRROLIDINOMETHYL) TETRACYCLINE*

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The production of N-(pyrrolidinomethyl) tetracycline (PMT) by the aminomethylation of tetracycline was first reported by Siedel, Soeder and Lindner[4] in 1958. The nature of its molecular structure was identified by Gottstein, Minor and Cheney[2] in 1959. This tetracycline derivative was found to be stable in the dry state with a water solubility 2,500 times greater than tetracycline hydrochloride (Siedel, Soeder and Lindner[4]). The antibacterial activities of N-(pyrrolidinomethyl) tetracycline were the same as the parent tetracycline (Fussgaenger[1]). Its structural formula is presented in Fig. 1.

Until the development of N-(pyrrolidinomethyl) tetracycline, the parenteral use of the tetracyclines was limited by their water insolubility and the moderate and severe subjective and objective reactions following intramuscular injection. Animal studies indicated that this new tetracycline derivative was less irritating to tissue (Hergott and Ther[3]). Data to be presented in this paper resulted from studies of tolerance, absorption, and excretion of N-(pyrrolidinomethyl) tetracycline following intramuscular injection.

Methods and Materials. The test antibiotic was formulated in a dry state and reconstituted in distilled water prior to use. Each

*Supplied by Bristol Laboratories, Division of Bristol-Myers Company, as Syntetrin.

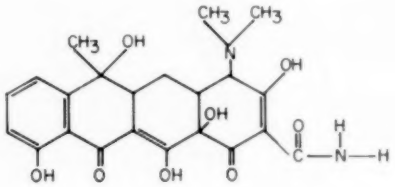
vial contained 40 mg. of lidocaine and 300 mg. of ascorbic acid in addition to the N-(pyrrolidinomethyl) tetracycline.

Healthy ambulatory adult volunteers were used in all absorption studies. The PMT was injected into the gluteal muscle using a 22-gauge needle 1¼ inches long. The first group of experiments was designed to determine the serum concentrations following single doses of the test antibiotic in amounts ranging from 143 mg. to 786 mg. Blood samples were withdrawn at 0, 1, 3, 8, and 24 hours and the serum was assayed for tetracycline content. Those subjects who received single injections of 178, 393, or 786 mg. collected all urine excreted over a 30-hour period in 6-hour units.

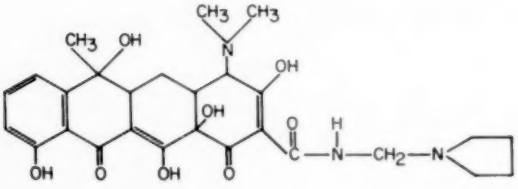
The second group of observations was made to determine the serum concentrations following repeated intramuscular injections of PMT. The dosages used in these experiments were: 178 mg. every 8 or 12 hours, 191.5 mg. every 12 or 24 hours, and 393 mg. every 8, 12, or 24 hours. Blood samples were withdrawn for tetracycline assay one hour after each injection and just before a repeat injection. The urine excreted by the volunteers receiving 178 mg. of the antibiotic every 8 or 12 hours was collected in 6-hour units for 120 hours. Hemograms, urinalyses, and blood-urea-nitrogen determinations were made at the beginning and end of the experiments where 393-mg. doses were used.

The tetracycline assays were performed by the cup plate method using *Bacillus cereus*, variety mycoides, as the test organism and PMT as the standard (970 μg. per ml.). The range of reproducibility of this assay in our laboratory is plus or minus 9%.

Results. *Single-dose experiments.* The average tetracycline serum concentrations following a single intramuscular injection of varying amounts of PMT are presented in Table 1 and Fig. 2. The test antibiotic is readily absorbed from intramuscular sites with mean one-hour levels increasing from 1.56 μg. per ml. to 11.5 μg. per ml. for the lowest (143 mg.) and highest (786 mg.) doses given. The tetracycline serum concentration at 24 hours ranged from 0 following a 143-mg. dose to 1.79 μg. per ml. following a 786-mg. dose. The serum concentrations at 24 hours following intermediate doses of PMT were essentially proportionate to the amount of antibiotic injected.



TETRACYCLINE



N-(PYRROLIDINOMETHYL) TETRACYCLINE

Fig. 1

TABLE 1.—BLOOD LEVELS OBTAINED FROM SINGLE DOSES OF N-(PYRROLIDINOMETHYL TETRACYCLINE (μg./ml.)

Dose	*No. Vol.*	*0 Hour*	*1 Hour*	*3 Hours*	*6 Hours*	*8 Hours*	*12 Hours*	*24 Hours*
143 mg.	5	0	1.56 (0.84–1.96)	1.06 (0.70–1.40)		0.81 (0.56–1.12)		0
178 mg.	15	0	2.25 (1.26–3.36)	1.55 (0.98–2.3)	1.32 (0.7–1.7)	1.09 (0.7–1.9)		0.16 (0–0.8)
191.5 mg.	30	0	2.28 (1.28–5.32)	1.24 (0.84–1.82)		0.98 (0.42–1.40)		0.32 (0–0.42)
214 mg.	5	0	3.55 (2.52–4.76)	2.38 (1.96–2.80)		1.79 (1.12–3.08)		0.36 (0–0.84)
235.8 mg.	10	0	4.00 (3.08–6.02)	2.64 (1.96–3.08)		1.72 (1.4–2.38)		0.65 (0.56–0.98)
250 mg.	5	0	3.36 (2.66–4.76)	2.19 (1.96–2.52)		1.56 (1.4–1.68)		0.61 (0.42–0.70)
275.1 mg.	10	0	4.50 (2.66–4.76)	2.87 (2.1–4.2)		2.08 (1 26–3.08)		0.71 (0.42–0.84)
286 mg.	5	0	3.98 (3.36–4.76)	2.63 (1.96–3.22)		1.79 (1.4–2.25)		0.64 (0.42–0.84)
357 mg.	10	0	4.67 (3.64–7.0)	3.12 (2.38–4.20)		2.54 (2.1–3.5)		0.84 (0.56–1.26)
393 mg.	45	0	6.32 (1.26–12.42)	3.54 (1.82–5.88)	2.96 (1.9–5.46)	2.28 (1.4–3.36)	1.72 (1.12–2.52)	1.23 (0.56–3.5)
786 mg.	5	0	11.5 (9.1–16.8)	8.23 (6.3–14.0)		5.51 (4.76–6.86)		1.79 (1.4–2.24)

The average tetracycline serum concentrations in Table 1 have been plotted as a log. function of the amount of PMT injected. Straight lines with one-sigma confidence bands are fitted to these points (Fig. 3). Within the limits of the doses studied, it would appear that the average amount of tetracycline activity in the serum can be predicted for a specified dose.

Multiple-dose experiments. Seven experiments were performed to establish the tetracycline serum concentration patterns following 178-mg., 191.5-mg., and 393-mg. doses (Table 2). The time intervals between injections were 8, 12, or 24 hours. Serum was withdrawn one hour after each injection in order to establish the highest tetracycline serum concentrations and just before each repeated injection in order to determine the lowest serum levels.

The average high and low tetracycline serum levels following multiple 178-mg. doses injected at 8- or 12-hour intervals are presented in Fig. 4.

AVERAGE SERUM TETRACYCLINE CONCENTRATION
AFTER SINGLE INTRAMUSCULAR INJECTIONS
OF N- (PYRROLIDINOMETHYL) TETRACYCLINE

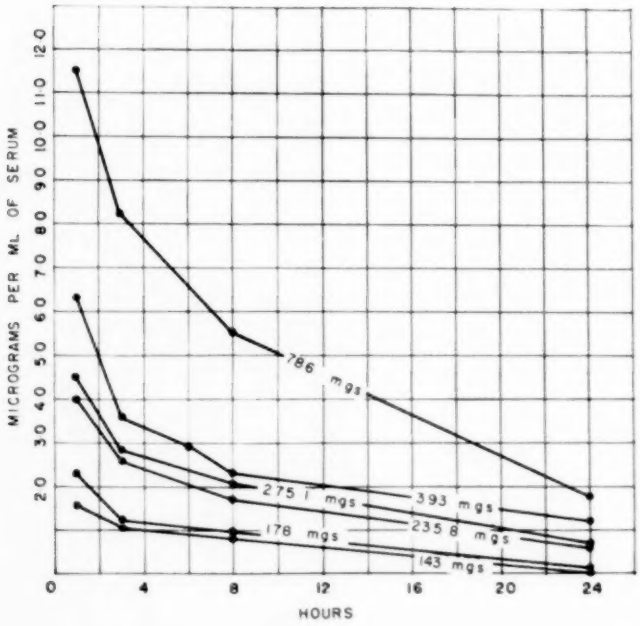


Fig. 2

On the 12-hour regimen, the average high antibiotic serum level was between 2 and 3 μg. per ml. and the lowest concentration was 1.0 μg. per ml., with little or no evidence of accumulation of antibiotic in the serum. When the time interval between injections was reduced to 8 hours, there was a progressive increase in both the low concentration (0.7 to 2.0 μg. per ml.) and the high concentration (1.6 to 3.5 μg. per ml.) during the administration of

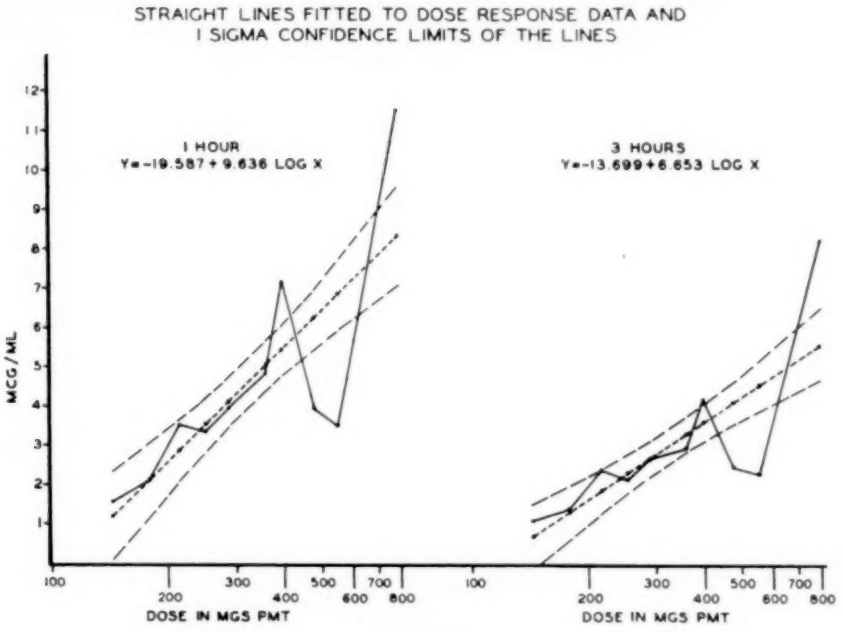


Fig. 3

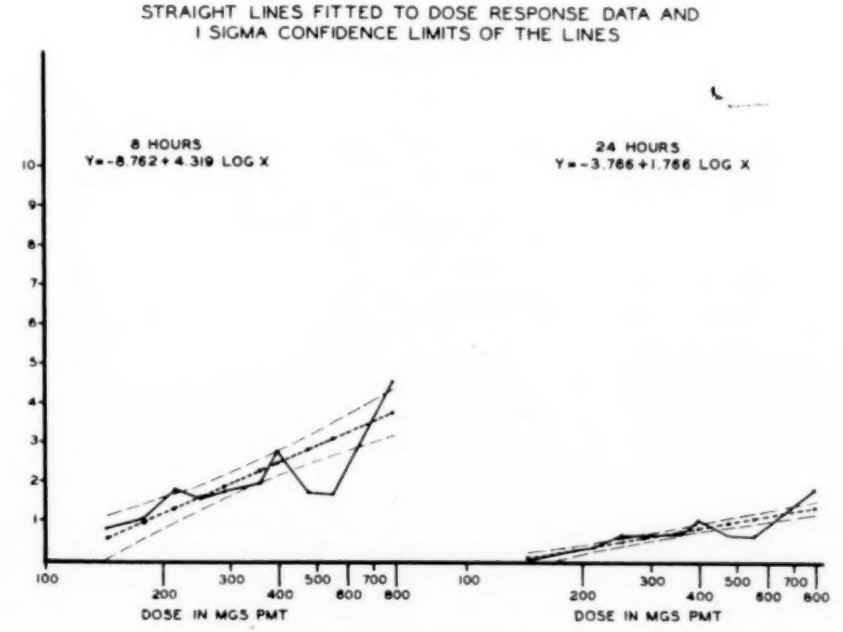

STRAIGHT LINES FITTED TO DOSE RESPONSE DATA AND
1 SIGMA CONFIDENCE LIMITS OF THE LINES
8 HOURS
Y=-8.762+4.319 LOG X
24 HOURS
Y=-3.786+1.786 LOG X
DOSE IN MGS PMT
DOSE IN MGS PMT

Fig. 3 *(continued)*

10 consecutive doses. The curve produced by the average high concentrations in both experiments paralleled the curve of the respective low concentrations.

of antibiotic was injected at 24-hour intervals, the average high concentrations in the serum ranged from 1.8 to 2.8 μg. per ml. without a consistent pattern of accumulation and the aver-

TABLE 2.—MULTIPLE-DOSE EXPERIENCE WITH N-(PYRROLIDINOMETHYL) TETRACYCLINE (μg./ml.)

No.	*178 mg. q8h*	*178 mg. q12h*	*191.5 mg. q12h*	*191.5 mg. q24h*
Subj.	5	5	10	10
Ave. Age.	28	42	29	34
Ave. Wt.	159	151	150	166
1 Hr.	2.24 (1.82–3.36)	2.29 (1.26–2.80)	1.95 (1.26–2.80)	2.84 (1.56–5.32)
3	1.42 (0.98–2.10)	1.59 (1.12–1.96)		
6		1.23 (0.98–1.40)		
8	1.03 (0.84–1.40)			
9	3.58 (2.38–5.32)			
12		0.81 (0.70–0.84)	0.76 (0.56–0.98)	
13		2.63 (2.1–3.08)	3.12 (1.7–5.04)	
16	1.62 (1.26–1.96)			
17	3.43 (2.66–4.06)			
24	1.98 (1.40–2.38)	1.12 (0.98–1.26)	1.13 (0.7–1.7)	0.42 (0–0.7)
25	3.57 (2.80–4.62)	2.94 (2.24–3.36)	3.62 (2.24–7.0)	2.67 (2.1–4.48)
32	2.12 (1.40–2.38)			
33	4.16 (3.86–5.32)			
36		1.40 (1.26–1.54)	1.45 (0.84–2.52)	
37		3.14 (2.80–3.68)	3.75 (2.52–5.88)	
40	2.32 (1.68–2.66)			
41	4.34 (2.80–5.32)			
48	2.66 (1.96–3.08)	1.42 (1.28–1.54)	1.54 (0.98–2.24)	0.56 (0.42–0.84)
49	4.28 (2.52–5.74)	2.84 (1.40–3.68)	3.70 (1.82–5.46)	2.67 (1.82–5.6)
56	2.53 (1.82–3.08)			
57	4.98 (3.36–6.86)			
60		1.34 (0.84–1.54)	1.41 (0.84–2.1)	
61		3.66 (3.08–4.62)	3.42 (2.24–4.9)	
64	2.77 (2.24–3.22)			
65	4.92 (4.34–6.02)			
72	2.85 (2.38–3.08)	1.45 (1.4–1.54)	1.40 (0.84–2.24)	0.58 (0.28–0.98)
73				3.32 (2.1–6.16)
80	1.68 (1.4–2.1)			
88	0.92 (0.7–1.12)			
96	0.64 (0.4–0.84)	1.45 (1.12–1.68)	0.28 (0–0.7)	0.63 (0.42–0.84)
97				3.33 (2.24–6.58)
120	0	1.51 (1.26–1.68)		0.71 (0.56–0.98)

Repeated intramuscular injections of 191.5 mg. of PMT every 12 hours produced average high antibiotic serum levels of approximately 2.5 μg. per ml. and average low concentrations of 1.0 μg. per ml. (Fig. 5). When this amount

age low concentration was 0.4 μg. per ml. As in the experiments using 178-mg. doses every 12 hours, there was no evidence of antibiotic accumulation in the serum.

The accumulation of tetracycline in

the serum following repeated injections of PMT was demonstrated in 3 experiments using 393-mg. doses at different time intervals (Fig. 6). When this amount of antibiotic was given every 24 hours, the average high and low serum concentration curves were parallel with each other and with the base line (average high, 5.0 to 5.5 μg. per ml.; low, 0.4 to 0.8 μg. per ml.). When the interval between injections was reduced to 12 hours, there was a gradual increase in the high and low serum levels with repeated doses. The average high level after the first dose was 4.4 μg. per ml. and after the sixth dose, 6.8 μg. per ml. The average low levels followed a similar pattern starting with 1.8 μg. per ml. 12 hours after the first dose and increasing to 2.8 μg. per ml. 12 hours after the last dose. This tendency for antibiotic accumulation became more pronounced when the interval between injections was reduced to 8 hours. Here the high tetracycline serum levels increased from a mean of 3.6 μg. per ml. after the first dose to a mean of 8.1 μg. per ml. after the sixth dose. The low concentration reflected closely the high concentration pattern, starting with an average of 1.5 μg. per ml. 8 hours after the first dose and increasing to 4.1 μg. per ml. 8 hours after the sixth dose.

TABLE 2.—MULTIPLE-DOSE EXPERIENCE WITH N-(PYRROLIDINOMETHYL) TETRACYCLINE (μg./ml.) *(Continued)*

	393 mg. q8h	*393 mg. q12h*	*393 mg. q24h*
No. Subjects	10	10	10
Average Age	30	37	40
Average Weight	159	135	143
1 Hour	5.11 (0.98–10.64)	5.60 (4.2–7.28)	7.29 (4.2–10.36)
3		3.10 (1.96–4.06)	
8	2.11 (0.28–4.34)	2.32 (1.68–3.08)	
9	7.53 (5.32–12.88)		
12		1.74 (1.26–2.52)	
13		7.11 (4.76–9.80)	
16	3.45 (5.52–6.02)		
17	7.75 (5.46–14.0)		
24	4.59 (3.08–7.98)	2.46 (1.68–3.08)	0.78 (0.42–1.12)
25	10.09 (7.0–21.0)	7.86 (5.88–9.66)	7.02 (4.2–9.52)
32	5.19 (3.64–9.24)		
33	10.02 (7.0–19.6)		
36		2.88 (1.96–3.92)	
37		8.40 (6.72–10.08)	
40	5.28 (4.06–11.62)		
41	11.32 (7.56–22.4		
48	5.88 (3.92–11.78)	3.38 (2.8–4.62)	0.88 (0.28–1.26)
49		7.16 (5.32–8.82)	7.25 (2.8–9.94)
56	3.43 (1.82–6.72)		
60		3.08 (2.38–3.5	
61		8.70 (6.3–11.76)	
64	2.08 (1.26–4.48)		
72	1.49 (0.56–2.80)	3.15 (2.1–3.92)	1.16 (0.56–1.4)
73			7.67 (4.76–9.8)
96	0.53 (0–0.84)	1.14 (0.7–1.82)	1.14 (0.7–1.82)
97			6.76 (1.54–9.24)
120		0.36 (0.28–0.56)	1.03 (0.56–1.40)

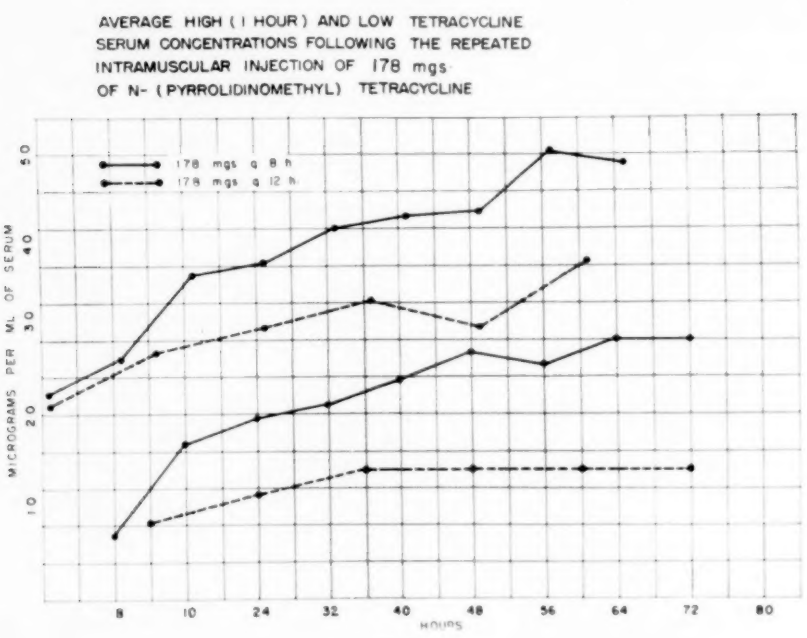

AVERAGE HIGH (1 HOUR) AND LOW TETRACYCLINE
SERUM CONCENTRATIONS FOLLOWING THE REPEATED
INTRAMUSCULAR INJECTION OF 178 mgs
OF N- (PYRROLIDINOMETHYL) TETRACYCLINE
178 mgs q 8 h
178 mgs q 12 h
MICROGRAMS PER ML OF SERUM
10
20
30
40
50
8
10
24
32
40
48
56
64
72
80
HOURS

Fig. 4

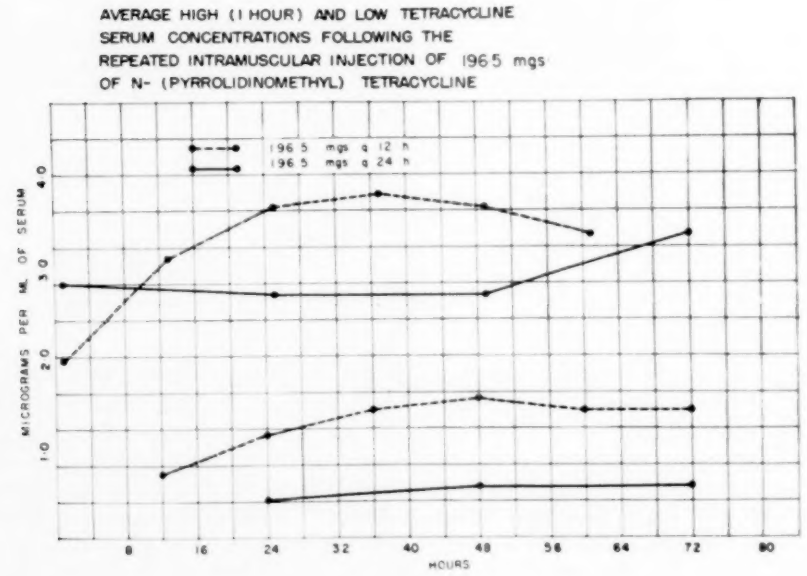

AVERAGE HIGH (1 HOUR) AND LOW TETRACYCLINE
SERUM CONCENTRATIONS FOLLOWING THE
REPEATED INTRAMUSCULAR INJECTION OF 196.5 mgs
OF N- (PYRROLIDINOMETHYL) TETRACYCLINE
196.5 mgs q 12 h
196.5 mgs q 24 h
MICROGRAMS PER ML OF SERUM
1.0
2.0
3.0
4.0
8
16
24
32
40
48
56
64
72
80
HOURS

Fig. 5

EXCRETION. The pattern of tetracycline excretion in the urine following single intramuscular injections of 178 mg., 393 mg., and 786 mg. of PMT is presented in Table 3 and Figure 7. An average of 20, 17, and 24%, respectively, of the total injected dose was recovered in the urine during the first 6 hours after administration; 11, 13, and 14%, respectively, was recovered in the second 6-hour collection; 9, 6, and 8%, respectively, was recovered in the third 6-hour collection; 7, 9, and 7%, respectively, was recovered in the fourth 6-hour collection, and 5% of each was recovered in the fifth 6-hour period. The total amount of tetracycline identified in the urine during the 30 hours of observation ranged from 50 to 60% of the total dose of PMT injected. Statistically, there is no difference among these excretion percentages.

The urinary excretion of PMT following repeated injections of 178 mg. of the antibiotic at 8- and 12-hour intervals is presented in Table 4 and Figure 8. There is considerable variation between samples; however, it can be seen that the average amount excreted in the first 6 hours is identical for both groups. As the test progressed, the urinary tetracycline concentration was greater in those subjects receiving PMT every 8 hours. The last dose was given at 72 hours to this group; the urine collected during the next 48 hours showed a gradually decreasing excretion of tetracycline. A total of 1,780 mg. of PMT was given to each group; 58% of this was recovered in the urine of those on the every-8-hour replacement schedule and 59% was recovered in the urine of those on the every-12-hour replacement schedule. The amount of tetracycline identified

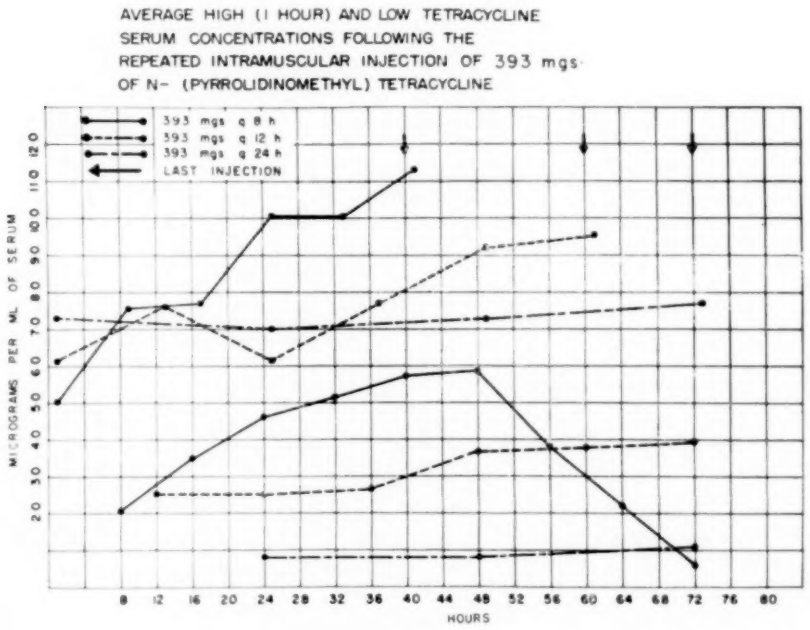

AVERAGE HIGH (1 HOUR) AND LOW TETRACYCLINE
SERUM CONCENTRATIONS FOLLOWING THE
REPEATED INTRAMUSCULAR INJECTION OF 393 mgs
OF N- (PYRROLIDINOMETHYL) TETRACYCLINE
393 mgs q 8 h
393 mgs q 12 h
393 mgs q 24 h
LAST INJECTION
MICROGRAMS PER ML OF SERUM
20 30 40 50 60 70 80 90 100 110 120
8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80
HOURS

Fig. 6

in the urine during the multiple-dose experiments was proportional to that observed following single-dose experiments.

TOLERANCE. The volunteers' subjective response to single or multiple doses of N-(pyrrolidinomethyl) tetracycline containing 40 mg. of lidocaine was uniform. There was very little discomfort at the time of injection; 15 to 20 minutes later, most subjects complained of moderately severe pain at the site of injection which persisted for 1½ to 2½ hours. After the pain

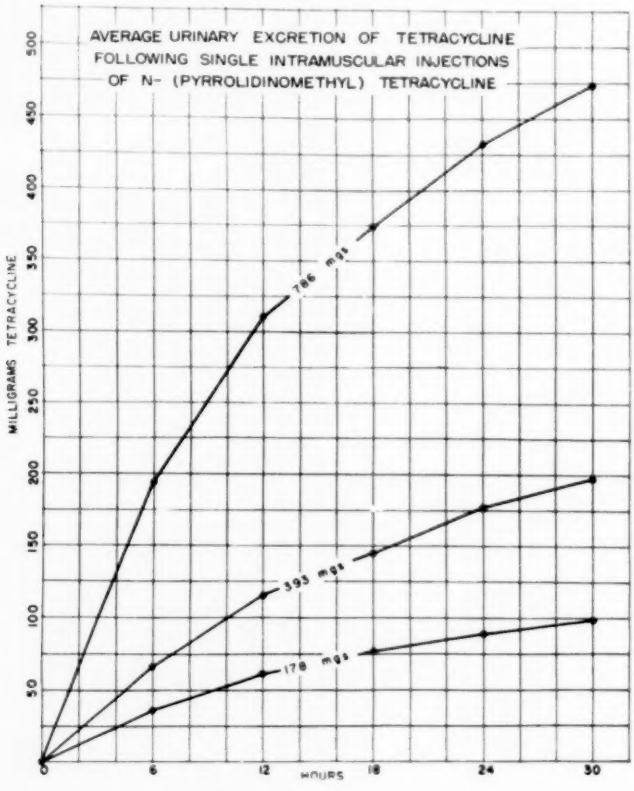


Fig. 7

TABLE 3.—AVERAGE AMOUNTS OF N-(PYRROLIDINOMETHYL) TETRACYCLINE EXCRETED IN THE URINE (μg./ml.)

	178 mg.	*393 mg.*	*786 mg.*
No. Subjects	5	5	5
0–6 Hours	36.89 (28.7–42.21)	65.27 (47.05–92.82)	194.12 (120.12–272.48)
6–12	20.70 (8.82–33.6)	51.07 (35.7–69.58)	116.76 (48.3–159.6)
12–18	16.49 (6.65–26.04)	23.21 (16.24–30.45)	62.70 (18.48–98.0)
18–24	13.44 (7.56–15.68)	37.94 (26.75–59.5)	58.60 (49.28–75.46)
24–30	9.18 (7.05–14.0)	20.43 (12.01–37.8)	41.13 (34.02–48.72)
Total	99.92	197.92	473.31
% of Dose	60	50	60

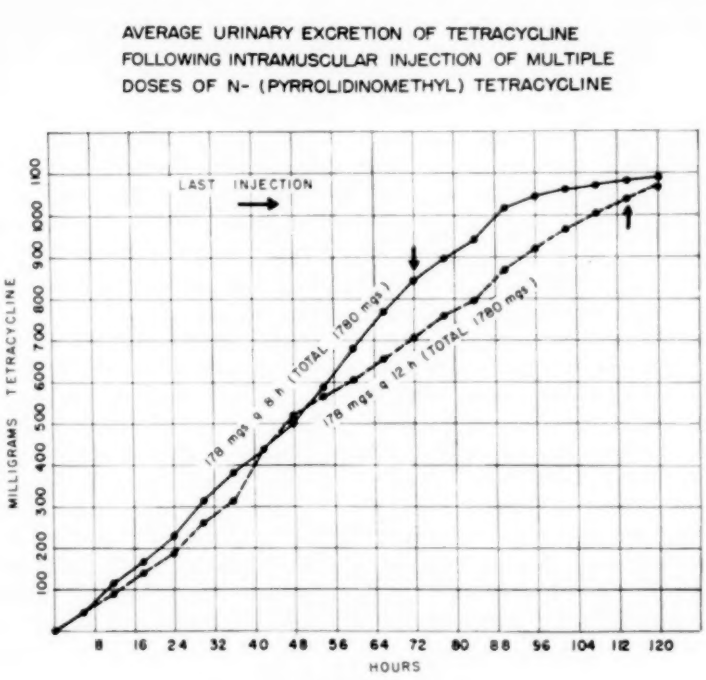

AVERAGE URINARY EXCRETION OF TETRACYCLINE
FOLLOWING INTRAMUSCULAR INJECTION OF MULTIPLE
DOSES OF N- (PYRROLIDINOMETHYL) TETRACYCLINE
LAST INJECTION
178 mgs q 8 h (TOTAL 1780 mgs)
178 mgs q 12 h (TOTAL 1780 mgs)
MILLIGRAMS TETRACYCLINE
100 200 300 400 500 600 700 800 900 1000
8 16 24 32 40 48 56 64 72 80 88 96 104 112 120
HOURS

Fig. 8

TABLE 4.—AVERAGE AMOUNTS OF N-(PYRROLIDINOMETHYL) TETRACYCYINE EXCRETED IN THE URINE AFTER MULTIPLE DOSES (μg./ml.)

	178 mg. q8h	*178 mg. q12h*
No. of Subjects	5	5
0–6 Hours	45.24 (30.1–67.2)	45.53 (39.2–59.5)
6–12	54.93 (44.1–70.56)	42.17 (11.66–97.21)
12–18	69.69 (63.7–84.49)	55.16 (44.66–65.1)
18–24	58.94 (47.32–70.0)	40.33 (30.59–58.24)
24–30	86.53 (39.9–134.4)	81.39 (41.16–169.05)
30–36	67.36 (21.28–80.92)	51.24 (21.07–102.20)
36–42	54.27 (23.1–80.64)	122.36 (39.69–254.10)
42–48	64.81 (32.13–79.13)	82.78 (15.68–257.60)
48–54	84.37 (63.17–115.43)	50.99 (28.66–58.24)
54–60	92.64 (71.82–126.35)	33.75 (25.0–50.40)
60–66	91.00 (56.70–120.12)	50.23 (42.82–67.20)
66–72	75.85 (60.06–93.38)	49.42 (28.21–71.82)
72–78	53.59 (20.37–70.0)	52.91 (22.07–79.80)
78–84	44.34 (35.17–49.98)	39.51 (7.98–62.37)
84–90	28.00 (16.44–38.52)	77.06 (49.98–111.02)
90–96	23.85 (14.8–43.68)	47.56 (35.70–67.20)
96–102	17.43 (2.77–48.59)	46.86 (35.0–56.7)
102–108	9.56 (7.42–11.10)	33.30 (25.38–40.42)
108–114	6.99 (3.0–11.43)	36.92 (8.4–69.44)
114–120	5.27 (3.24–6.76)	26.55 (10.85–40.56)
Total Excretion	1,034.76	1,066.02
Percent of Dose	58	59

stopped, pressure discomfort could be elicited for several hours. There was little, if any, subjective reaction 24 hours after injection and there was no objective evidence of tissue reaction at or around the injection site. This general pattern of discomfort was observed regardless of the size of dose injected. There was, however, less pain following the injection of 178 mg. or 191.5 mg. than following the injection of 357 mg. or 393 mg.

Several volunteers were injected with PMT without lidocaine. Within one minute after the injection these subjects experienced moderate to severe pain which lasted 2 to 3 hours. The pain experienced following PMT without lidocaine was much more severe in intensity than that experienced following PMT with lidocaine.

With the exception of local discomfort, there was no other evidence of side reactions. A comparison of hematocrits, hemoglobins, white blood counts, blood-urea-nitrogens, and serum creatinines before and after multiple 393 mg. doses of PMT revealed no significant changes.

Discussion. Through hundreds of studies since 1948, the various tetracycline antibiotics have become well-established as bacteriostatic agents for a wide range of Gram-negative and Gram-positive bacteria as well as for Rickettsia and some of the Rickettsia-like organisms generally included in the "Large Viruses." During the accumulation of this mountain of literature, it has been demonstrated repeatedly that all of the tetracyclines are absorbed with reasonable efficiency from the gastrointestinal tract. The ease with which tetracycline is thus absorbed is complemented by the fact that most tetracycline-sensitive microorganisms are inhibited by serum concentrations obtained in this manner.

The need for a parenteral formulation of the various tetracyclines has been and is infrequent, even though the amount sold belies this statement. The various intramuscular formulations of oxytetracycline, chlortetracycline, tetracycline hydrochloride, and tetracycline phosphate complex produce local tissue reaction and pain of such severity that the physician cannot continue the drug, even if the patient were willing.

Even though the need for an intramuscular form of tetracycline is not frequent, it is conceivable that such situations could occur. The possible elements of this theorectical situation are: an infection with a tetracycline-sensitive microorganism in which the host's gastrointestinal tract is unavailable as a route of administration or an infection with a microorganism which is only relatively sensitive to tetracycline and unusually high serum concentrations are required for inhibition. It should be determined that the microorganisms involved are not sensitive to a more acceptable antibiotic such as penicillin; if they are, parenteral tetracycline should be used only if the patient has a known allergy to penicillin. If it can be decided from sound laboratory data that parenteral tetracycline is the antibiotic of choice, then N-(pyrrolidinomethyl) tetracycline can be used with safety, reasonable acceptance by patients, and reliable therapeutic expectancy.

Summary and Conclusions. 1. The absorption and excretion of a highly soluble tetracycline, N-(pyrrolidinomethyl) tetracycline, from intramuscular sites has been presented. Single doses ranging from 143 mg. to 786 mg. and multiple doses ranging from 178 mg. to 393 mg. were used.

2. The average tetracycline serum concentration following a single injection of 143 mg. was 1.56 μg. per ml. at 1 hour and 0 at 24 hours. The aver-

age serum concentration following a single injection of 786 mg. was 11.5 μg. per ml. at 1 hour and 1.79 μg. per ml. at 24 hours. The average concentrations obtained with intermediate doses were proportionate to the amount of antibiotic injected.

3. Repeated intramuscular injections of the antibiotic at 8- and 12-hour intervals produced increasing concentrations of tetracycline in the serum. When the injections were spaced at 24-hour intervals, the antibiotic did not accumulate in the serum.

4. Between 50 and 60% of the tetracycline injected was recovered in the urine during the first 30 hours regardless of the amount injected (approximately 20% during the first 6 hours, 13% during the second 6 hours, 8% during the third 6 hours, 8% during the fourth 6 hours, and 5% during the fifth 6 hours).

5. N-(pyrrolidinomethyl) tetracycline administered intramuscularly is relatively well-tolerated when compared with other intramuscular tetracyclines. There was no evidence of cellulitis at injection sites, as was commonly seen following the injection of tetracycline hydrochloride or tetracycline phosphate complex.

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SUMMARIO IN INTERLINGUA

Le Absorption e Excretion de N-(Pyrrolidinomethylo)-Tetracyclina

1. Es reportate le absorption e excretion de un solubilissime tetracyclina, N-(pyrrolidinomethylo)-tetracyclina, ab sitos intramuscular. Doses unic de inter 143 e 786 mg e doses multiple de inter 178 e 393 mg esseva usate.

2. Le concentration seral medie de tetracyclina post le injection unic de 143 mg esseva 1,56 μg per ml a 1 hora e 0 a 24 horas. Le concentration seral medie post le injection unic de 786 mg esseva 11,5 μg per ml a 1 hora e 1,79 μg per ml a 24 horas. Le concentrationes medie obtenite con doses intermediari esseva proportional al quantitate de antibiotico injicite.

3. Repetite injectiones intramuscular del antibiotico a intervallos de 8 e 12 horas produceva crescente concentrationes de tetracyclina in le sero. Quando le injectiones esseva intervallate per 24 horas, nulle accumulation esseva notate in le sero.

4. Inter 50 e 60% del tetracyclina injicite esseva retrovate in le urina durante le prime 30 horas, sin reguardo al quantitate injicite (approximativemente 20% durante le prime 6 horas, 13% additional durante le secunde 6 horas, 8% durante le tertie 6 horas, 8% durante le quarte 6 horas, e 5% durante le quinte 6 horas).

5. N-(pyrrolidinomethylo)-tetracyclina, administrate per via intramuscular, es relativemente ben tolerate in comparation con altere tetracyclinas intramuscular. Esseva constatate nulle evidentia de cellulitis al sito del injection, como il esseva le caso communmente post le injection de hydrochloruro de tetracyclina o de phosphato de tetracyclina complexe.

ROUTINE URINE CULTURES IN PRIVATE PRACTICE*

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Are routine urine cultures feasible and justifiable in a private practice of internal medicine? The frequency of asymptomatic bacteriuria, particularly in women, has been recorded in numerout reports (Table 1) (Boshell and Sanford[3], Kass[7,8], Loopuyt[9], Marple[11], Merritt and Sanford[12], Switzer[14]). However, the patients selected for most of these studies have been either hospitalized or outpatients representing a medically indigent population and as such may not be representative of a private practice. The observations by Kass of significant bacteriuria in only 0.5% of a group of female college students and by Switzer of an incidence of 3% in Japanese women routinely followed by the Atomic Bomb Casualty Commission suggest a lower incidence in ambulatory patients who are less selected than patients comprising the earlier groups (Boshell and Sanford[3], Kass[7]).

The feasibility of screening either male or female patients for asymptomatic bacteriuria by the use of "sterile-voided" mid-stream urine collections combined with some technique of quantitative bacterial enumeration also has been demonstrated both in hospitalized patients and in outpatient clinics associated with teaching centers. Such techniques are essential if routine screening cultures are to be performed since 2 to 3% of females develop infection after urethral catheterization and thus might exceed the incidence of asymptomatic bacteriuria (Beeson[2], Guze and Beeson[4], Marple[11]). However, the feasibility of "sterile-voided" urine cultures in a practice has been seriously questioned (Annotation[1]).

The present studies were undertaken to ascertain the feasibility of "sterile-voided" urine cultures in a practice of internal medicine as well as the frequency of asymptomatic bacteriuria in

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a group of ambulatory, non-indigent female patients of an age distribution seen in an unselected practice.

Materials and Methods. "Sterile-voided" specimens were obtained from 100 unselected ambulatory female patients seen in a practice limited to internal medicine (R.K.B. and R.B.McB.). Their reasons for seeking medical attention were variable; however, none presented with primary urinary tract symptoms. The nurse instructed the patient to cleanse the perineum with hexachlorophene liquid soap (PhisoHex) and to collect the midstream urine in a sterile bottle. The specimens were immediately placed in a refrigerator and quantitative cultures performed in most instances within 24 hours, none over 48 hours after collection.

Quantitative bacterial counts were carried out by making 2 successive 10-fold dilutions of the urine in 0.9% saline solution. One milliliter (ml.) of the 10^{-2} (1:100) and the 10^{-3} (1:1000) dilutions were pipetted onto sterile petri dishes. Approximately 10 ml. of melted, cooled, tryptic digest agar (Baltimore Biological Laboratories) was added and mixed by swirling. The contents of the pour plates were allowed to cool and solidify, then inverted and incubated at 37° C. for 24 to 36 hours. The bacterial colonies were then counted under magnification in a Quebec colony counter.

After removal of an aliquot of urine for quantitative bacterial count, approximately 0.2 ml. of urine was pipetted into 10 ml. of tryptose broth (Difco). Standard biochemical fermentation reactions and cultural characteristics were used for the identification of the bacterial strains isolated.

Results. The frequency of varying degrees of bacteriuria in these patients is recorded in Table 2. "Significant" bacteriuria, variously defined as "sterile-voided" urines containing greater than 50,000 to 100,000 bacteria per ml. of urine, was demonstrated in only one patient (1%). This patient was asymptomatic, nulliparous, had no past history to suggest renal disease and had never been catheterized.

The majority of patients (78%) were over 40 years of age. This age distribution is similar to that in groups of hospitalized female patients where an incidence of asymptomatic bacteriuria of 14 to 15% was observed (Boshell and Sanford[3], Merritt and Sanford[12]).

Various clinical features which might be anticipated to correlate with bac-

TABLE 1.—FREQUENCY OF ASYMPTOMATIC BACTERIURIA IN FEMALE PATIENTS

Author	*Type of Patient*	*Percentage with "Positive" Cultures*
Marple[11]	Hosp.	23
Loopuyt[9]	Hosp.	29
Kass[7]	Hosp.	30
	OPD	6
Kass[8]	Students	0.5
Merritt[12]	Hosp.	14
Boshell[3]	Hosp.	15
Switzer*[14]	"Normal"	3

*Individuals were under routine surveillance by Atomic Bomb Casualty Commission in Japan.

TABLE 2.—BACTERIAL COLONIES PER ML. OF URINE

Age	*No. Pts.*	<10,000	10–50,000	50–100,000	100–500,000	>500,000
10–20	1	1				
20–40	21	16	4		1	
40–60	44	38	6			
>60	34	31	3			
Total	100	86	13	0	1	0

teriuria including the presence of hypertension or a past history of urinary tract disease were present in 18 patients (Table 3). Seven patients had sustained diastolic hypertension; however, 6 had less than 10,000 bacteria per ml. of urine. The seventh patient, who also had a diagnosis of chronic pyelonephritis, had 20,000 bacteria per ml. of urine. Of the 12 patients with a past history of urinary tract disease, none had "significant" bacteriuria. The 2 patients with chronic pyelonephritis neither had been on recent treatment nor had had recent symptoms. The uncommon. A sterile or essentially negative voided urine culture (approximately 10,000 bacteria per ml. or less) has the same significance as a culture obtained by catheterization. Though it has been estimated that 5% of patients with low degrees of bacteriuria actually have chronic pyelonephritis, this phase would remain elusive by either voided or catheterized urine collection (Jackson, Grieble and Knudsen[6], Yow *et al.*[15]). A urine containing more than 50,000 to 100,000 bacteria per ml. is strongly suggestive of bacteria within the urinary tract rather than contamina-

TABLE 3.—CLINICAL FEATURES IN 18 PATIENTS

Clinical Feature	*No. of Patients*	*Degree of Bacteriuria (colonies/ml.)*				
		0–1000	1001–10,000	10,001–20,000	20,001–30,000	30,001–40,000
Hypertension†	7	6		1		
Prev. Urinary Sx*	5	4	1			
Chronic Pyelo.†	2	1		1		
Prev. Acute Pyelo.	2		1		1	
Urethral Caruncle	1	1				
Renal Calculi	1		1			
Albuminuria	1		1			

*Urinary tract symptoms including dysuria, frequency or urgency
†One patient was both hypertensive and had a diagnosis of chronic pyelonephritis

patient with renal calculi still had a stone in the right kidney. The 2 patients with acute pyelonephritis had had only a single previous attack.

Thus, asymptomatic bacteriuria was infrequent (1%) in this series of 100 ambulatory female patients despite a history of antecedent urinary tract symptoms or renal disease in 12 patients.

Discussion. This study demonstrates that the collection of voided-urine specimens from female patients for quantitative bacteriological study is as feasible in practice as has been demonstrated in hospitalized patients or in outpatient clinics associated with teaching centers. As noted previously, variable degrees of contamination during the collection of urine specimens is not tion during collection. However, with preliminary evidence of a significant degree of bacteriuria, either careful supervised repetition of a sterile-voided urine collection or catheterization is advisable before undertaking extensive urological or bacteriological diagnostic and therapeutic regimens.

The incidence of asymptomatic bacteriuria in this group of patients is considerably lower than that demonstrated either in hospitalized female patients or in ambulatory medically indigent outpatients. MacDonald and co-workers found that true bacteriuria (defined by them as greater than 100,000 bacteria per ml. of urine) correlated well with the presence of pyelonephritis in an unselected group of necropsies performed on adults[10]. While the role of

inapparent pyelonephritis in the genesis of chronic pyelonephritis with hypertension and renal insufficiency is still unknown, the studies of Kass suggest that therapy may be effective in eliminating or controlling asymptomatic bacteriuria (Kass[8], Sanford[13]). Thus, the routine performance of urine cultures as a screening procedure might be indicated since the frequency of asymptomatic bacteriuria reported in middle-aged female patients varies from 6 to 30% and pyelonephritis has been found in 6 to 20% of necropsies (Jackson, Dallenbach and Kipnis[5]). The observations reported in this study, as well as those of Switzer from Japan, suggest that the yield from the routine performance of urine cultures on all ambulatory female patients presenting for medical attention would be considerably lower than anticipated from earlier studies.

Summary. 1. The technique of sterile-voided urine collections combined with a quantitative culture technique has been practical for the collection of specimens from females for bacteriological study in a medical practice.

2. Significant bacteriuria was detected in only one of 100 unselected, ambulatory, non-indigent female patients. This frequency is lower than observed in most other studies in which either hospitalized or medically indigent patients were studied.

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SUMMARIO IN INTERLINGUA

Routinari Culturas de Urina in le Practica Private

1. Le technica del collection de urina sterilemente vacuate, combinate con un technica de culturation quantitative, se ha provate practic in le collection de specimens ab patientes feminin pro studios bacteriologic in un practica de medicina private.

2. Grados significative de bacteriuria esseva detegite in solmente un inter 100 non seligite, ambulante, e non indigente patientes feminin. Iste frequentia es plus basse que illo observate in le majoritate del altere studios in que patientes hospitalisate e/o patientes de stato indigente esseva le objecto del investigation.

THE FAMILY OF HYPERTENSIVE MAN
PROGRESS REPORT OF A LONG-RANGE STUDY PROGRAM*†

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Investigators have been looking at the family of man (hypertensive, that is) ever since Morgagni noted the familial occurrence of apoplexy, a disorder which killed his teacher's teacher, Malpighi. Subsequent to the advent of the sphygmomanometer, the published articles on the sisters and the cousins of hypertensives can be reckoned by the dozens. There are studies of single families, measurements of blood pressure in twins, analyses of family histories and examinations of relatives of patients with and without hypertension and belonging to many ethnic groups. The results can be illustrated best by the authoritative statements of those concerned. These range from the conclusion that an hereditary factor is not established (Allan[1]) to positive claims that hypertension is inherited as a Mendelian dominant (Platt[7]).

A new wave of enthusiasm rolled onto the hypertensive beach last winter and spring, in fact a new geography and vocabulary. The behavior of London bus-drivers and Moscow telephone operators, and their kith and kin, was aired at a symposium in Czechoslovakia (Joint World Health Organization[2]). Following the proposition of Pickering and his colleagues[3,4] that blood pressure is a continuous variable like height, came words such as "multifactorial" and "bimodality," curves like the backs of dromedaries and camels, even a few pungent letters to the editors. It is the quantitative problem of blood pressure rather than the qualitative presence of primary hypertension as a disease, they suggest, which leads to trouble.

Almost every study bearing on familial or genetic factors can be criticized. Clinical impressions and clusters of involved relatives prove little more than that accidents may occur in the best of well-regulated families. Conclusions have been drawn too frequently from small and selected series. More-

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over, the definition of hypertension has varied enormously, systolic pressures or single casual pressures have been employed at times, and little distinction has been made between primary and secondary hypertension. Hearsay evidence, and the inclusion of sudden death or cardiovascular accidents as the sole proof of an elevated blood pressure, have been incorporated into many studies of family history. Controls have been lacking or have been selected, with conditions dissimilar to those of index cases. Finally, just as epidemiological studies of blood sugars might fail to segregate all the diabetics, so those who record blood pressures may be closing their eyes to the evolution of what others regard as a definite disease.

Although handicapped as yet by the absence of a satisfactory diagnostic test, we believe that primary (essential) hypertension is a specific disease[5]. Among the arguments are its peak onset in early middle age, at times abruptly, the smooth contours of the curve of onset in relation to age, and two clear-cut populations of blood pressure when multiple casual readings are secured and averaged (Perera[6]). It is also our contention that no one has either established or ruled out a genetic factor, although many of us have the clinical impression that heredity plays an important rôle. The continued disagreement and confusion indicate clearly that there are wide gaps in our knowledge and that there is urgent need to identify those characteristics which, in association with the presence or absence of a familial tendency, lead to the maintenance of normotension or to the development of hypertension.

Is primary hypertension more prevalent among relatives of hypertensives? Are there differences in individual qualities and environmental factors? What are the relative rôles of heredity and environment?

To seek answers to these questions we are investigating 100 patients with documented primary hypertension and 100 control normotensives, all past middle age, all matched for equality, all with a living spouse and two or more siblings or offspring, or both. The index cases, controls and families are being subjected to detailed interview, thorough examination, and diagnostic tests to exclude secondary causes of hypertension or disturbances which might mask or modify hypertension. We are prying into every aspect of heredity, health, habits, housing and host factors, past and present, clinical and climatological, and are recording blood pressure and sundry laboratory data under a variety of conditions. We are fortunate to have the assistance of technicians, biostatisticians and epidemiologists at every level of formulation, design and interpretation.

This is in the nature of a preliminary report of our progress and problems, mostly the latter. Anyone who believes it is possible to determine quickly the prevalence or nature of hypertension in the Congo, Korea or Cooperstown, even with the help of a full team and an adequate budget, is, we learned in short order, open to question. We began by facing difficulties in the conditions of the experimental design. Definitions had to be made and the cooperation of families and physicians had to be secured. Friendly persuasion was the order of the day. To find the 100 documented index cases and an equal number of controls is requiring a search involving approximately 6,000 persons. We have discovered that not

everyone knows his age, that matrimony and parenthood are sometimes dissociated, and that ethnic origin is multiple or uncertain in many instances. More important, we have found that a complete history, a thorough physical examination and appropriate laboratory studies are an insufficient basis for a diagnosis of normotension or hypertension in 15 to 20% of cases studied at any one point in time. We speak not only of those normal or labile individuals who may yet develop hypertension at a later date (they can be followed), but of those with borderline values in whom a prospective search may be fruitless. Take, for example, a 60-year-old man with a vague history of high blood pressure, a touch of angina, casual and resting readings in the 160/90 range and a one-plus proteinuria. Even if primary renal disease can be excluded, was he a hypertensive with lower values because of a silent myocardial infarction? Is he a normotensive with an inelastic aorta, and a circulation responding to anxiety? It is doubtful that time will tell. Fortunately, the records of family physicians and of hospitals and clinics, combining the retrospective approach as well, clarify many but not all of these situations. It will take several years at least to complete even our immediate objectives; it remains to be seen whether ultimate ones can be achieved.

It is too early to tell of our data on the rôle of occupation, hobbies, enuresis and weight, on the rôle of false teeth, shared kitchens, blue eyes and green salads, but they are all on the list. What are the facts we have learned thus far?

As of this date 46 families, or more than 200 persons, have been studied in fairly complete detail. Of 22 families in which both parents are normotensive, not a single one of their 41 children has an elevated blood pressure, although 6 of a total of 25 siblings are hypertensive. On the other hand, of 24 families with one hypertensive parent, 3 of their total of 32 children and 14 of their total of 30 siblings have established primary hypertension. But keep in mind that many of the young ones have not passed the age before which hypertension might yet appear. Even with these small numbers, there is a definite familial concentration which may prove to be statistically significant as the study progresses. Primary hypertension seems to be approximately twice as common in hypertensive as compared with normotensive families.

This study also affords an opportunity to learn something about the prevalence of primary hypertension. Unless there are peculiarities in the ways in which normotensives and hypertensives select their mates, based on millimeters of mercury rather than on equivalents of Venus, a clue as to prevalence can be obtained by noting the condition of the spouses of our index and control cases. The numbers are still too small to be meaningful, but 4 of the hypertensives and 2 of the normotensives have found an hypertensive partner.

What of the few families with 2 hypertensive parents? They, contrasted to the previous groups, may provide ultimately the only direct evidence of an hereditary factor. A clue is apparent already, for the majority of their adult offspring are hypertensive, but as yet there are far too few such families to hold up in any scientific court. And even if we progress so as to establish a genetic factor, and we believe we may, is it the disease which is inherited, or merely a predisposition made manifest by environmental factors? Time may tell, for we believe that no one has approached the problem using a comparable study design, and our study is barely under way.

If nothing else is clear to us, it is that, despite a voluminous literature, the part played by inherited and acquired factors in the genesis of primary hypertension remains obscure. We can, however, take a more positive position. In our minds some new laws are emerging from investigations such as these. They begin to read as follows: 1) the more common and chronic a disorder, the longer it will take to obtain established facts regarding it, and 2) the more common and chronic a disorder, the more difficult it will be to evaluate the rôles of nature, nurture and nostrums.

The path ahead is long and difficult, much more so than has been realized to date, but we are convinced that a climb up the family tree will net us some nutritious fruit. Perhaps some day we will learn how to prune its hypertensive branches.

Summary. Despite a voluminous literature, the part played by inherited and acquired factors in the genesis of primary hypertension remains obscure. A long-range study is described in which 100 patients with documented primary hypertension and 100 control normotensives, all past middle age, all matched for equality, all with a living spouse and 2 or more siblings or offspring, or both, are being investigated. Although the study is only in its preliminary stages, a definite familial concentration is evident already. The difficulties in undertaking such a study are described; it remains to be seen whether the rôle of inheritance and environment can be defined clearly.

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SUMMARIO IN INTERLINGUA

Le Familia del Homine Hypertensive
Reporto de Progresso in un Programma de Studios a Longe Vista

In despecto del voluminose litteratura concernite con ille thema, le rolos que factores hereditabile e factores acquirite ha in le genese de hypertension primari remane obscur. Es describite un studio a longe vista in que 100 patientes con documentate hypertension primari e 100 subjectos normotensive como gruppo de controlo—omnes de etates in ultra del medie vita e omnes appareate sub varie criterios e omnes con conjuges vive e al minus 2 fraternos o procreatos o ambes—es le objectos del investigation. Ben que le studio es ancora in su stadios preliminari, un definite concentration familial es jam evidente. Es describite le difficultates incontrate in un studio de iste genere. Si o non le rolo del hereditate e le rolo del ambiente pote esser definite clarmente e differentialmente remane a vider.

CIRCULATORY EFFECTS OF PIPE AND CIGAR SMOKING*

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Much attention has been devoted to the effect of smoking cigarettes on the circulation but relatively little information is available on the circulatory action of pipe and cigar smoking. Such information seems important because of the large amount of tobacco consumed in the United States in these forms. In 1955, it was estimated that there were 8.8 million pipe smokers; the current annual consumption of pipe tobacco is nearly 75 million pounds. In 1955, there were 10.6 million cigar smokers; in 1959, almost 6.75 billion cigars were smoked (Sackrin and Conover[18], U.S. Dept. of Agriculture[22]). In 2 recent reports of mortality experience of nearly 400,000 men, although an increased death rate from carcinoma of the lung and heart disease was noted in heavy cigarette smokers, the death rate in regular cigar or pipe smokers, or those who smoke both cigars and pipe, was not appreciably higher than that of non-smokers (Dorn[6], Hammond and Horn[10]). Therefore, it seemed worthwhile to gather data on the circulatory changes caused by smoking regular commercial and low nicotine cigars and pipe tobacco and to compare the results with our own and other previous studies on cigarette smoking and chewing tobacco (Maddock, Malcolm and Coller[15], Roth, McDonald and Sheard[17], Simon *et al.*[20,21], Wright and Moffat[24]).

Method of Study. The subjects in this study were 25 habitual male smokers. Fifteen subjects smoked cigars and 10 smoked pipes; their ages ranged between 21 and 69 years. Eight subjects were studied while sham smoking unlit pipes or cigars under identical conditions. Studies were carried out in the basal post-absorptive state on each subject on 3 separate days. On one day low nicotin tobacco was smoked in a constant temperature room, and on another day regular tobacco was smoked. On a third day the effect of high nicotine tobacco on the ballistocardiogram was determined; the order of studies was variable. Skin temperatures were measured in a constant temperature room at 78° F. (25.6° C.) and 40% relative humidity from copper-constantan thermocouples attached to the forehead and the volar surfaces of the fingers and toes, employing a Brown constant recording potentiometer. Changes of 0.5° C. were considered significant. Blood pressures and pulses were obtained by the usual clinical methods. The ballistocardiograms were recorded with a high frequency table-type research instrument (Braunstein, Oelker and Gowdy[3]). The subjects were supine and unclothed and rested for at least 45 minutes prior to smoking. The period of smoking was 20 minutes. Subjects smoked at their habitual rates and none inhaled the smoke. The com-

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mercial cigars were a well known brand containing 1.82% nicotine (moisture free basis) (Bennett[2]). The low-nicotine cigars were commercially available† containing 0.88% nicotine. The pipe tobacco used was a commercial brand containing 2.15% nicotine (moisture free basis) (Hanmer[11]). Pipe tobacco containing 0.72% nicotine was used for the low nicotine studies.‡

The low nicotine cigars weighed 6.6 gm., the regular cigars weighed 6.5 gm. A pipeful of tobacco weighs approximately 2.0 gm. For comparison, a standard cigarette contains 1 gm. of tobacco and approximately 20 mg. (2%) nicotine (Chemical Laboratory[4]).

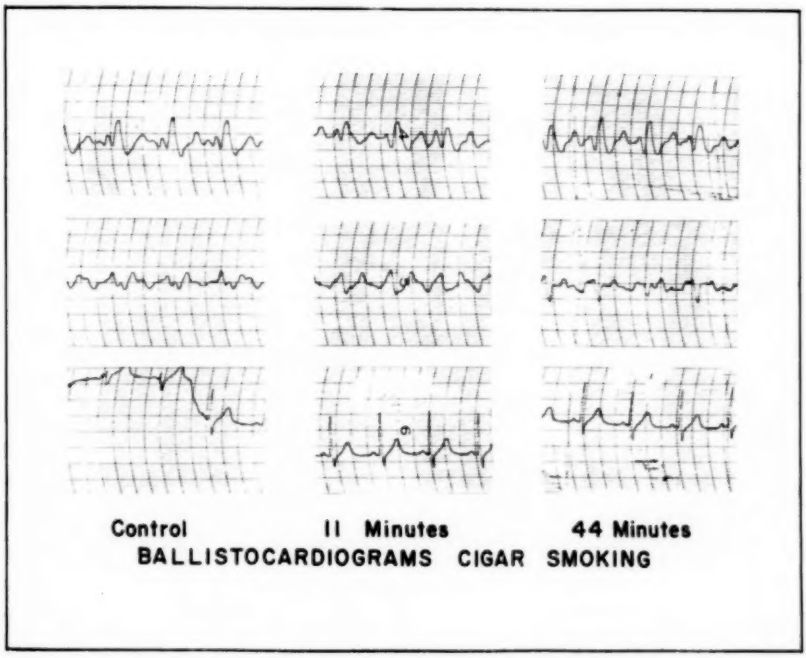

Fig. 1.—Effect of cigar smoking on ballistocardiogram. Top row: Longitudinal component. Middle row: Side to side component. Bottom row: Lead I Electrocardiogram. Normal complexes (control) change to early M pattern (row I) 11 minutes after start of smoking; normal pattern reappears 24 minutes after end of smoking.

Results. BALLISTOCARDIOGRAMS. *Cigars.* Studies were made in 12 subjects while smoking commercial cigars. In 9 of these men, ballistocardiograms were normal before smoking: 3 remained normal throughout the smoking period and after smoking; 3 showed records with abnormally increased respiratory variation. The remaining 3, however, showed greater changes from normal, either in the form of early M or late downstroke patterns (Fig. 1).

The records of the other 3 subjects were abnormal before smoking. In 2 of these, the abnormality increased during and after smoking, and in one it lessened. The maximum changes occurred within 10 to 20 minutes of the start of smoking and persisted for 20 to 30 minutes or longer.

Pipes. Ten subjects were studied

†Supplied by U.S. Tobacco Co.
‡Supplied by U.S. Tobacco Co.

while smoking commercial tobacco. The ballistocardiograms of 8 were normal before smoking. Records of 3 of these remained normal throughout; 3 showed only minor changes, consisting either of minor respiratory variation or changes in the amplitude of the complexes. Two showed rather marked abnormality after smoking with development of a definite early M pattern (Fig. 2).

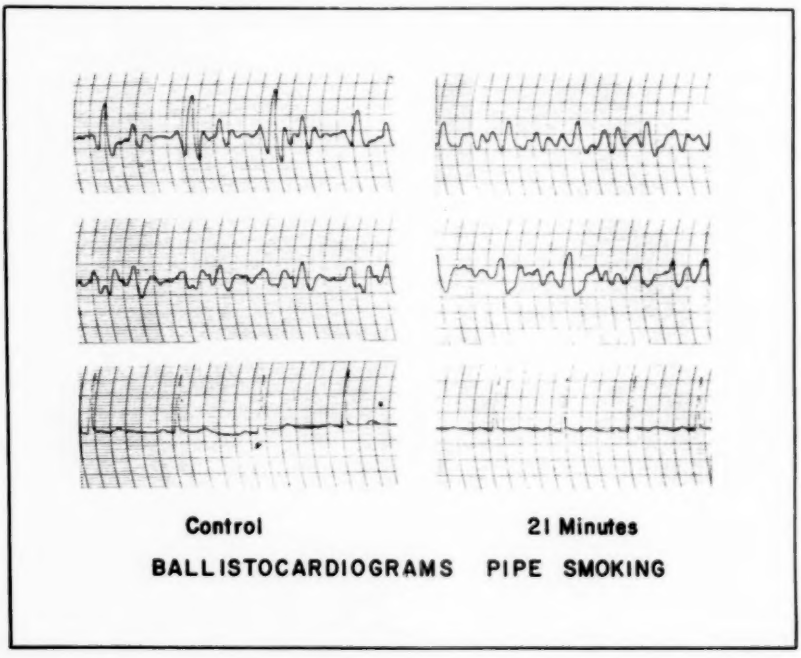

Fig. 2.—Effect of pipe smoking on ballistocardiogram. Top row: Longitudinal component. Middle row: Side to side component. Bottom row: Lead I Electrocardiogram. Normal complexes noted during control period become abnormal showing an early M type pattern at end of smoking period.

In 2 subjects who smoked pipes, the records were abnormal before smoking. In one of these, the record showed only minimal changes during smoking but in the other the abnormalities became more marked. The changes occurred in from 10 to 20 minutes and persisted for 20 or 30 minutes or longer.

PULSE RATE. *Cigars.* The pulse rates were counted in 15 subjects who smoked both high and low nicotine content cigars. In all of the subjects smoking commercial cigars, the pulse rate increased; the maximal increase varied from 1 to 12 beats per minute. The average of these maximal increases was 6.4 beats per minute. During the smoking of the low nicotine cigars, the pulse rate increased in 14 subjects, the maximal change being from 1 to 15 beats more per minute. In one subject the pulse rate decreased slightly. The average of maximal changes in these subjects was +5.3 beats per minute (Fig. 3).

Pipes. Ten subjects smoked regular and low nicotine tobacco in pipes.

During the smoking of the regular commercial tobacco, 9 subjects showed an increase in pulse rate; maximum increase varied from 3 to 20 beats per minute. In one subject the rate decreased 4 beats per minute. Average of maximal changes was +7.4 beats per minute. While smoking low nicotine tobacco the pulse rate increased in 7 subjects; maximal increase ranged from 2 to 12 beats per minute. In 2 subjects, the heart rate decreased 4 and 10 beats per minute and in one the rate remained unchanged. The average of maximal changes was +4.2 beats per minute (Fig. 3). Maximal changes in the pulse rate occurred from 2 to 30 minutes after the start of smoking.

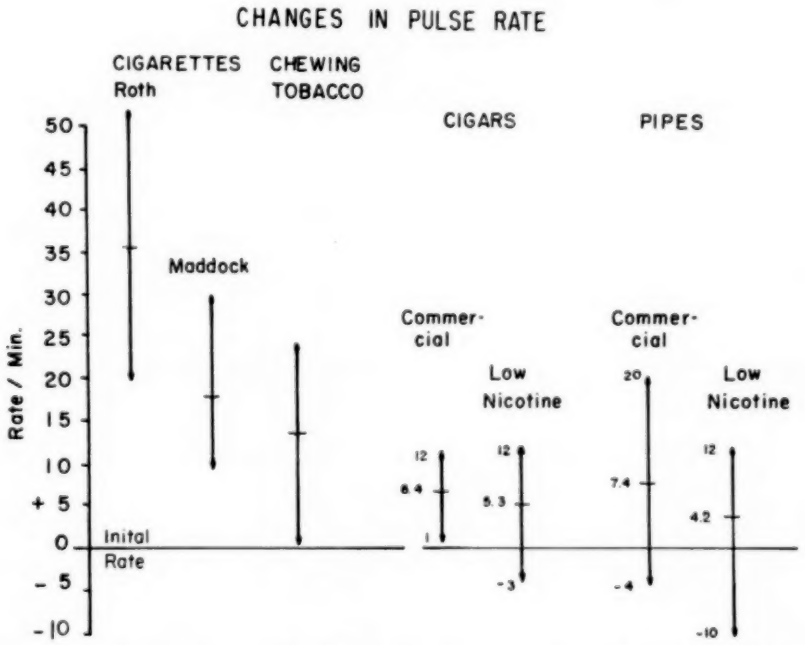

Fig. 3.—Changes in pulse rate. Results of present study indicated on right half of graph. For comparison, changes following cigarette smoking and tobacco chewing left half of graph. Mean of changes indicated by horizontal cross bars. Range of maximum change indicated by vertical arrowed lines (see text).

BLOOD PRESSURES. *Cigars.* Fifteen subjects smoked regular and low nicotine cigars. All subjects showed an increase in both systolic and diastolic blood pressure while smoking regular cigars. The maximum systolic blood pressure increase ranged from 2 to 12 mm. Hg (mean of increase 7.3 mm. Hg). The maximum diastolic blood pressure increase varied from 2 to 18 mm. (mean of increases 8.9 mm. Hg).

During the smoking of low nicotine cigars, systolic blood pressure increased in 11 subjects, range of maximum increase 1 to 15 mm. Hg. In 3 there was no change in systolic blood pressure, and in one the systolic blood pressure decreased. The average of maximal change was +4 mm. Hg. The diastolic blood pressure increased in all subjects with an average maximal increase of 6.3 mm. Hg, range 1 to 16 mm.

Pipes. Blood pressures were measured in 10 subjects while smoking regular commercial and low nicotine tobacco in pipes. During the smoking of high nicotine tobacco, the systolic and diastolic blood pressure increased in all subjects. The average of maximal increases was 9 mm. systolic and 8 mm. diastolic with a range of 1 to 18 mm. Hg in both. During the smoking of low nicotine tobacco in pipes, systolic blood pressure increased in 5 subjects, decreased in 2 and remained unchanged in 3. Diastolic blood pressure increased in 7 of these patients and decreased in 3 (Fig. 4).

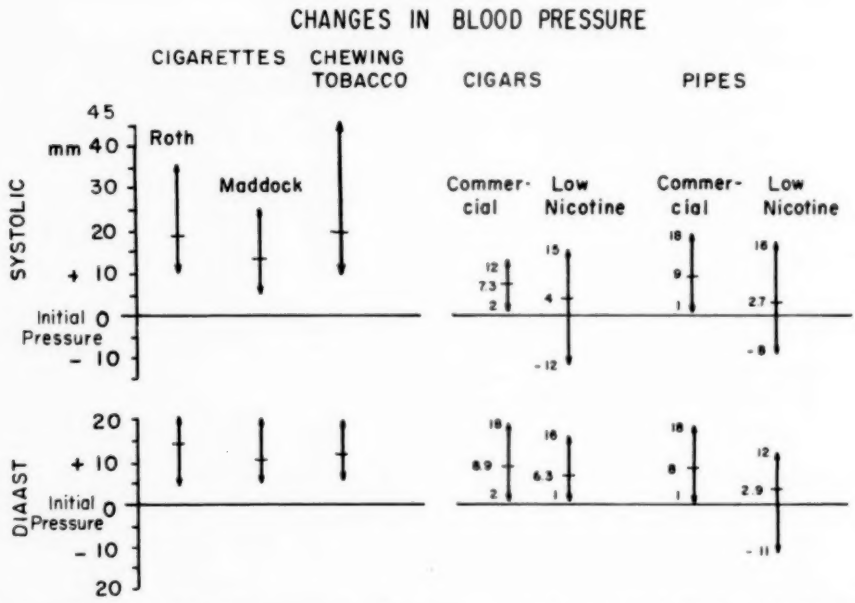

Fig. 4.—Changes in blood pressure. Results of present study on right half of graph. Cigarette and chewing tobacco changes on left for comparison.

SKIN TEMPERATURES. *Cigars.* Skin temperatures were measured in the fingers and toes of 15 subjects who smoked regular commercial cigars. The average initial temperature of the fingers was 32.3° C. Skin temperatures fell in 12 of the subjects, remained unchanged in one and increased slightly in 2. These changes are presented graphically in Fig. 5. Eleven subjects were studied with low nicotine cigars. The initial fingertip temperatures averaged 32.5° C. In 9 subjects, the skin temperatures decreased, and in 2 subjects, changes were equivocal (Fig. 5). In both groups of observations, the toe temperatures did not show any consistent pattern of change. Forehead temperature did not change.

Pipes. Skin temperature observations were made on 10 subjects while smoking regular commercial tobacco in pipes. The average initial temperature of the fingers was 33.2° C. Finger temperatures decreased in 9 of the subjects and in one subject changes were equivocal (Fig. 6). Nine subjects were studied with low nicotine tobacco. The average initial finger temperature was 33.9° C. Finger temperatures decreased

in 8 of the subjects, and in one subject changes were equivocal (Fig. 6). No consistent pattern of changes was noted in the feet.

Forehead temperature did not change. Maximal changes in skin temperatures occurred from 9 to 50 minutes after the start of smoking.

no significant change in pulse rate, blood pressure or ballistocardiograms. In most of these subjects changes did occur with actual smoking.

Discussion. In our own study[20] and that of Henderson[12] of the ballistocardiogram during smoking cigarettes, no changes were observed in healthy

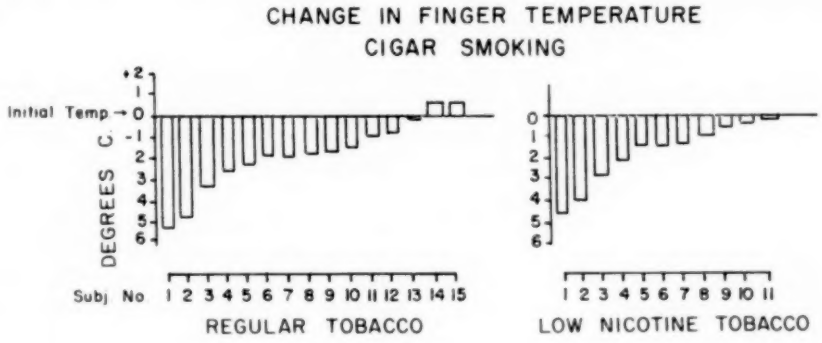

Fig. 5.—Maximal changes of skin temperature: average of 4 fingers.

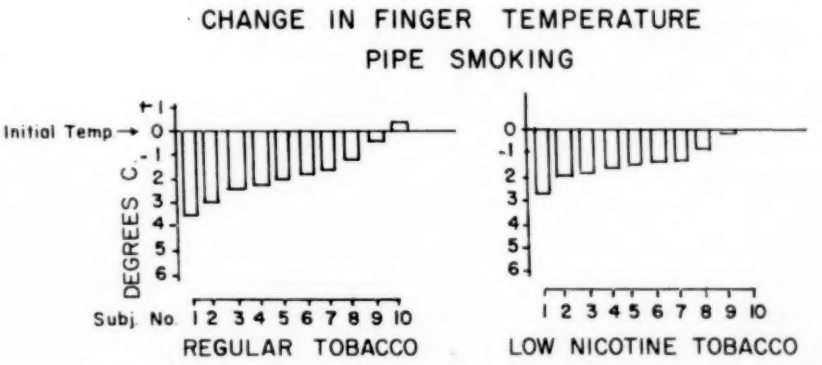

Fig. 6.—Maximal changes of skin temperature: average of 4 fingers.

The averages of changes with cigar and pipe smoking were almost identical. Greater decrease in finger temperature occurred in a few cigar smokers (Fig. 7).

SHAM SMOKING. Eight subjects who puffed unlit cigars or pipes, under the same experimental conditions, showed

young males. Other observers have found changes in a small proportion of healthy and abnormal subjects while smoking cigarettes (Dock, Mandelbaum and Mandelbaum[5], Levy *et al.*[13]). In contrast, abnormalities of the ballistocardiogram appeared or increased in 23 of 24 subjects who chewed tobac-

co (Simon *et al.*[21]). Abnormalities of the ballistocardiogram occurred or increased in 8 of 12 subjects after smoking cigars and in 6 of 10 subjects after smoking pipes. Thus, the incidence of ballistocardiographic change with pipe and cigar smoking was higher than that observed with cigarette smoking, but lower than that observed with chewing tobacco.

Although systolic and diastolic blood pressure increased in all subjects who smoked regular commercial cigars, the changes were less than those generally noted with smoking cigarettes and tobacco chewing (Maddock, Malcolm and Coller[15], Roth, McDonald and Sheard[17], Simon *et al.*[20,21], Wright and Moffat[24]). The blood pressure changes were less marked and less consistent

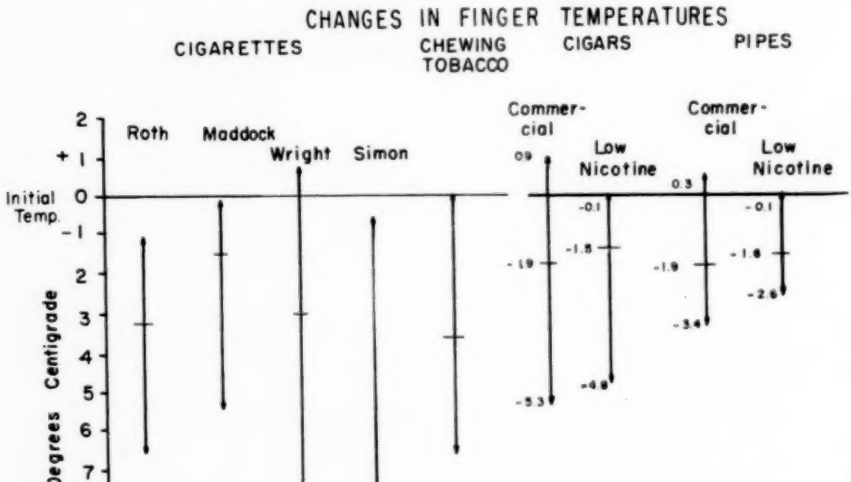

Fig. 7.—Comparative changes in finger temperatures. Present result (right). Previous studies (left).

Increases in pulse rate while smoking cigars were rather moderate in comparison with those reported by Roth, McDonald and Sheard[17], after smoking 2 cigarettes, and in comparison with our own findings with chewing tobacco[21]. Little difference was found between the regular and low nicotine cigars. The increases in pulse rate while smoking either regular or low nicotine tobacco in pipes were less than while smoking cigarettes or chewing. No significant difference was noted between pipes and cigars.

Skin temperature changes after smoking regular cigars and pipe tobacco were about equal, with slightly greater decrease during cigar smoking. If our findings are compared with the reported studies of Roth, McDonald and Sheard[17], Engelhardt and Stüttgen[7] and Maddock, Malcolm and

Coller[15], of skin temperature changes produced by cigarette smoking, the patterns are similar, with slightly greater decreases in cigarette smokers. When the changes following cigar and pipe smoking in the present study are compared with our previous study of chewing tobacco[21], it is found that maximum changes were slightly greater following tobacco chewing.

In contrast to the subjects in previous studies of cigarette smokers, none of our subjects inhaled. Previous studies are not in agreement as to the percentage of nicotine absorbed by smokers who do not inhale. The most frequently cited work, that of Baumberger[1] in 1923, indicates a high percentage of nicotine absorption, even without inhaling (66 to 77%). A more recent study by Greenberg, Lester and Haggard[9] indicated that without inhaling a smaller percentage of nicotine content of smoke is retained in the body. They found 4% to 45% of the nicotine was retained in smokers who did not inhale, whereas 96% to 98% was absorbed in subjects who inhaled. This raises the question of the effect of the respiratory activity alone during smoking on the circulation.

Mulinos and Shulman[16] found that deep breathing could produce transient vasoconstriction in the hands. However, none of our pipe or cigar smokers inhaled or breathed deeply. Many previous observers: Roth, McDonald and Sheard[17], Maddock and Coller[14], Wright and Moffat[24], Weatherby[23] have shown that sham smoking produced negligible changes in skin temperatures, pulse rates and blood pressures. More recent studies by Freund[8] were confirmatory. Furthermore, Weatherby[23] found quite inconsistent, small and variable changes in actual respiration during the act of smoking. In our own studies of sham smoking, no changes were found even in subjects who showed changes while smoking.

Thus, the present study indicates that failure to inhale does not prevent appearance of the usual circulatory effects of nicotine. Very few previous studies of pipe and cigar smoking were found. Maddock and Coller[14], in a few subjects, found following pipe smoking that pulse, blood pressure and skin temperature changes were similar to cigarette smokers. According to Scott[19], nicotine levels in the blood were lower after cigar or pipe smoking than after cigarette smoking.

It should be pointed out that the amount of nicotine available for absorption varies with such factors as moisture content, combustion temperature, length of filtration, loss through expectoration, as well as the obvious factors of nicotine content of tobacco smoked and rate of smoking.

Summary and Conclusion. 1. Ballistocardiograms, blood pressure, pulse rates and skin temperatures were studied in volunteer cigar and pipe smokers during and after smoking.

2. The usual effects of tobacco smoking on the circulation were found (namely, increase in pulse and blood pressure, drop in skin temperature), but were not as marked as usually found following cigarette smoking or chewing tobacco.

3. The incidence of changes in the ballistocardiograms in this study was less than that found following chewing tobacco, but greater than that found following cigarette smoking.

4. The circulatory effects of cigar and pipe smoking were approximately the same.

5. Circulatory changes were slightly less following low nicotine cigars and pipes when compared to standard cigars and pipes.

6. Sham smoking did not produce circulatory changes.

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SUMMARIO IN INTERLINGUA

Effectos Circulatori del Fumar Pipas e Cigarros

1. Ballistocardiogrammas e determinationes del tension de sanguine, del frequentia del pulso, e del temperaturas cutanee esseva studiate in voluntarios fumatores de cigarro e de pipa durante e post le fumar.

2. Le usual effectos del fumar de tabaco esseva trovate in le circulation—i.e. acceleration del pulso, augmento del tension sanguinee, e reduction del temperatura cutanee—sed illos esseva minus marcate que lo que es usualmente trovate post le fumar de cigarrettas o post le mastication de tabaco.

3. Le incidentia de alterationes del ballistocardiogramma in iste studio esseva plus basse que illo trovate post le mastication de tabaco sed plus alte que illo trovate post le fumar de cigarrettas.

4. Le effectos circulatori del fumar le pipa e del fumar cigarros esseva approximativemente le mesmes.

5. Le alterationes circulatori esseva levemente minus marcate post le fumar de cigarros o de tabaco de pipa a basse contento de nicotina que post le fumar del correspondente productos standard.

6. Le fumar fictitie—i.e. fumar a sic—non produceva ulle alterationes circulatori.

THE OCCURRENCE OF L.E. CELLS AND HEMATOXYLIN BODIES IN THE NATURALLY OCCURRING CUTANEOUS LESIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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The purpose of this paper is to report the occurrence of lupus erythematosus (L.E.) cells and hematoxylin bodies in naturally occurring skin lesions of acute disseminated lupus erythematosus. Ever since Hargraves, Richmond and Morton's original description of the production of the L.E. cell[8] this phenomenon has largely been regarded as one occurring *in vitro* (Hargraves[7], Harvey *et al.*[9]). L.E. cells have, however, been demonstrated in certain *in vivo* situations. These have included their demonstration in the blister fluid produced by the application of cantharides to the skin of patients with acute disseminated lupus erythematosus (Watson, O'Leary and Hargraves[22]); in direct blood films taken from the fingers of patients with systemic lupus erythematosus following constriction with a rubber band Sickley *et al.*[21]); by the experimental production of L.E. cells following application of L.E. factor (serum from a patient with S.L.E.) to the abraded skin of normal subjects (Rebuck and Berman[19]); in the incubated pericardial fluid of a patient with systemic lupus erythematosus (Seaman and Christerson[20]); in postmortem specimens of various organs (Gueft[6], Klemperer[12], Navarro-Martin and Garcia-Blanco[16]); in the smears of freshly drawn untreated peripheral blood in a terminal case prior to death (Chomet *et al.*[2]); and in Hargraves report of the occurrence of cells resembling L.E. cells in a splenic biopsy of a patient with S.L.E.[7].

Hargraves[7] points out objections to considering certain of these above examples as being true *in vivo* phenomena. He states "It may be said that all necropsy material has had a varying period *in vitro* after the victim's death and until biochemical activity is stopped by tissue fixation. The same might be said about blister fluid, pleural and peritoneal exudates and other fluids which have yielded L.E. cells or hematoxylin staining bodies.". This same concept may be applied to the instance in which L.E. cells were produced following the constriction of the fingers of the patients with S.L.E. by a rubber band. The authors point out that a number of abnormal conditions are

present such as anoxia and stasis. These conditions accompanied by incubation would produce a model situation similar to the *in vitro* technique of demonstrating L.E. cells.

Hematoxylin bodies have been described as reddish purple, amorphous bodies usually ovoid or spindle shaped with an approximate size of a nucleus or cell. They occur in tissue singly, in clusters, or coalesced into aggregates (Worthington, Baggenstoss and Hargraves[23]). These bodies have been mainly found at necropsy and have been useful as being highly specific for the postmortem diagnosis of S.L.E. when occurring in groups (Worthington, Baggenstoss and Hargraves[23], Klemperer *et al.*[13]). Hematoxylin body has been considered an *in vivo* phenomenon especially since its description in the promptly formalin fixed kidney biopsy specimens in cases of lupus nephritis reported by Muehrcke *et al*[15]. Prunieras and Montgomery studied cutaneous lesions in 38 cases of systemic lupus erythematosus[18]. They found, in addition to changes in the basement membrane and an intense macrophagic activity of connective tissue, intracellular bodies termed "red-bodies" which they attributed to depolymerization of deoxyribonucleic acid occurring in lymphocytic nuclei and in the nuclei of connective tissue cells. It was proposed that these were a possible early stage in the development of hematoxylin bodies. That they were not hematoxylin bodies is evident since the bodies did not take the PAS reaction. They were, however, Feulgen positive. The hematoxylin bodies, of course, are reddish purple in hematoxylin and eosin stain and although they are Feulgen positive, the hematoxylin body takes the PAS reaction avidly (Godman, Dietch and Klemperer[5]). It is felt that the L.E. factor or factors are responsible for both the production of L.E. cells and their tissue counterpart, the hematoxylin body.

Regardless of whether the L.E. cell is considered as occurring *in vitro* alone or both *in vitro* and *in vivo*, its occurrence in the natural lesions of S.L.E. is uncommon, and to our knowledge, has not been reported in a naturally occurring skin lesion. Since L.E. cells have been found in the experimental blister fluid of patients with S.L.E., their occurrence in the base of naturally occuring blisters of S.L.E. is not unexpected. The conditions necessary for the L.E. cell production; L.E. factor, phagocytic neutrophilic polymorphonuclear leukocytes, and nuclear material, are present in both situations.

Case Report. CASE 1. D.D., a 42-year-old white woman, was admitted to the Edward J. Meyer Memorial Hospital on April 10, 1959, with a chief complaint of severe progressive muscular weakness of 2 months' duration. This was associated with dysphagia, hoarseness and alopecia of 2 months' duration. On the day of admission she noted malaise, cough, chills, and fever. There was a past history of recurrent angioneurotic edema since childhood; spinal meningitis at age 15; bullous skin eruption at age 27; a positive serologic test for syphilis at age 37, treated with penicillin; a "nervous disorder" treated with electro-convulsive therapy at age 40; and an illness similar to the one on this admission followed by a "sunburn" like rash on the face that lasted several months at age 41. She had ingested many proprietary drugs in large quantities for many years.

Physical examination revealed an acutely ill, somewhat confused, adult white woman with a temperature of 102° F. rectally. Pulse was 104, blood pressure was 140/80, and respirations were 16 per minute. There was pronounced weakness of all extremities. She was unable to extend her right arm or either leg upon the trunk. The left arm was extended with difficulty. The muscles of the arms were slightly tender and those of the left thigh were quite tender. The voice was hoarse. A mottled dusky erythema was present over the extensor surfaces of the knuckles, elbows, knees, and toes. Several 2 to 4 mm. smooth, shiny, non-tender, firm nodules were present over several interphalangeal joints. Serous, crusted lesions were also present over the

elbows, several knuckles, and the lips. The skin of the face exhibited telangiectasis, old atrophic scars and a brown pigmentation without any induration. The scalp showed many atrophic scars and the scalp hair was coarse, particularly along the anterior hairline. The skin of the trunk showed dozens of anetoderma (macular atrophy) lesions (Fig. 1). Anetoderma is defined as atrophic oval patches located particularly on the trunk. The skin is thin, bluish-white and bulges slightly. These lesions give to the palpating finger the same sensation as does a hernial orifice. There are 2 types, the primary type of Schweninger and Buzzi, and the secondary type seen following lupus erythematosus, syphilis, and leprosy. In both types there is loss of elastic tissue and fat may infiltrate the area and bulge to resemble soft tumors (Ormsby and Montgomery[17], Andrews[1]). Several of the anetoderma lesions ballooned outwardly. The right pupil reacted poorly to light. The neck resisted flexion. The lungs were clear and the heart was regular with a grade two systolic murmur audible at the base. Definite left costovertebral angle tenderness was present. The abdomen was soft although she complained of diffuse tenderness. Pelvic and rectal examinations were normal. All joints were normal. The neurologic

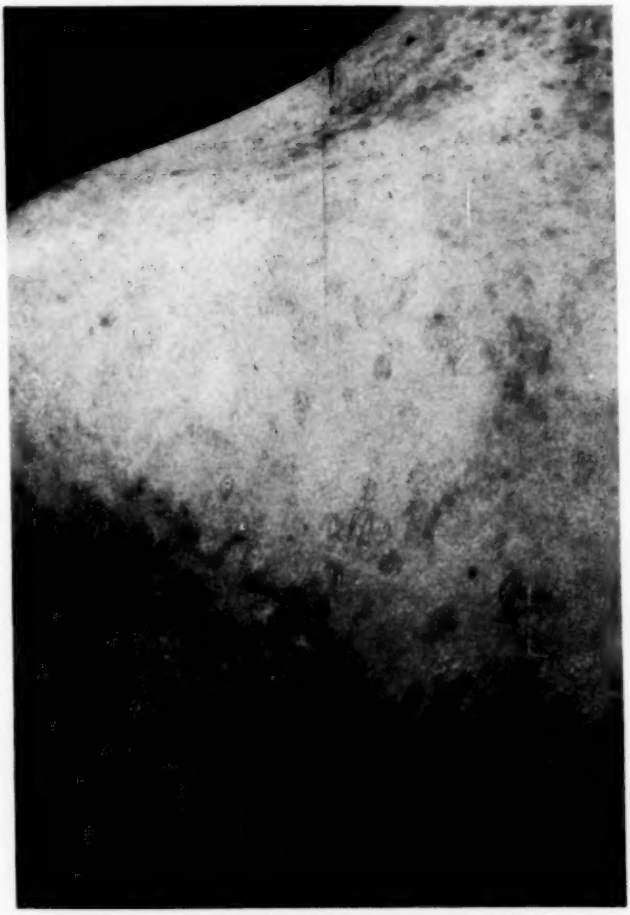

Fig. 1.—Typical anetoderma lesions of the trunk (See text).

examination was normal except for the neck and pupils as described above. No lymphadenopathy was noted. Lumbar puncture performed on admission showed a normal pressure with 792 fresh red blood cells per c.mm. Initial laboratory examination included a hematocrit of 29; hemoglobin of 9.6 gm.%; reticulocyte count, 0.8%; white blood cell count of 1,200 per c.mm. with a differential count of 2 band neutrophils, 64 segmented neutrophils and 34 lymphocytes. The platelet count was 280,000 per c.mm. The sedimentation rate was 29 (Wintrobe method). The L.E. cell preparation contained many L.E. cells (clotted blood method) (Fig. 2). The Wassermann was anticomplimentary. The protein electrophoretic pattern showed decreased albumin and increased alpha 1, alpha 2 and gamma globulins, the majority of which was in the gamma fraction. The total protein was 7.0 gm.% with an A/G ratio of 3.4 to 3.6. Both the direct and indirect Coombs tests were positive. Cold agglutination was negative. The cryoglobulins were slightly positive, and the Witebsky-Rubin test was positive. The patient cells in her own serum showed 3 plus agglutination at refrigeration temperature, one plus at room temperature, plus-minus at incubator temperature (see Table 1). The transaminases were normal. Urinalysis showed 2 plus albuminuria and a moderate number of white blood cells, and a rare red blood cell. Twenty-four hour creatinine excretion was 1.4 gm.; and creatine excretion for 24 hours was 0.64 gm. Urine urobilinogen was 0.2 Ehrlich unit and a trace of bile was present. Skin biopsy of the crusted lesions (Fig. 3) taken at the time of admission, April

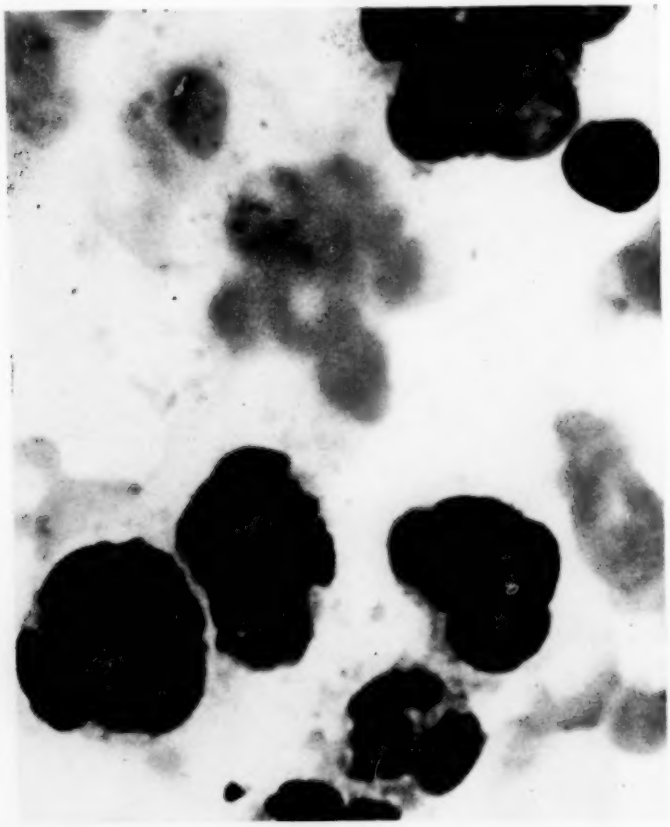

Fig. 2.—Typical L.E. cells by clotted technique from patient D.D. × 1200.

TABLE 1.—SEROLOGY ON CASE (D.D.)

Before Treatment: Cold Agglutination	Coombs		Witebsky-Rubin*			Patient's Cells in Own Serum		
	Dir.	*Indir.*	*Time in Min.*	*Serum Albumin*	*A-B Serum*	*ref.*	*rm. temp.*	*3.75°*
Negative	+	+						
	+	+	2	+		+++	+	±
			4.5		+			
			5	++	not intensifying			
			8.5	+++				
Repeat After Treatment:	+	Neg.		Neg.	Neg.		+	

Legend: — no agglutination
± equals faint agglutination
\+ equals slight agglutination
++++ equals very strong agglutination
+++ equals strong agglutination
++ equals marked agglutination

*The Witebsky-Rubin Test (reported in Proceedings of the Fourth International Congress of the International Society of Hematology printed in the U.S.A.) makes use of the fact that when albumin or, even better, a mixture of equal amounts of 30% bovine albumin and serum is used as a diluent against the patient's (unknown) serum and cell suspension, RH, iso- and simple autoantibodies of considerable titer may be demonstrated. In other diluents such as saline or normal serum, these antibodies may go unrecognized. It is felt by the authors that the simultaneous use of these 3 diluents (saline, normal adult serum, bovine serum-albumin mixture) reveals differences in iso-antibody and perhaps auto-antibody functions.

Fig. 3.—View of right elbow showing crusted skin lesion and biopsy site (Arrow).

10, 1959, and fixed promptly at the time of biopsy in formalin showed many typical L.E. cells in an extravascular position (Fig. 4). Hematoxylin bodies were seen in the same sections.

By the day following admission an erythematous rash occurred on both palms. Therapy was begun with intravenous ACTH which was continued for 10 days. Prednisone p.o. was initiated on the eighth hospital day. The fever and toxic state abated and considerable initial improvement occurred. The patient

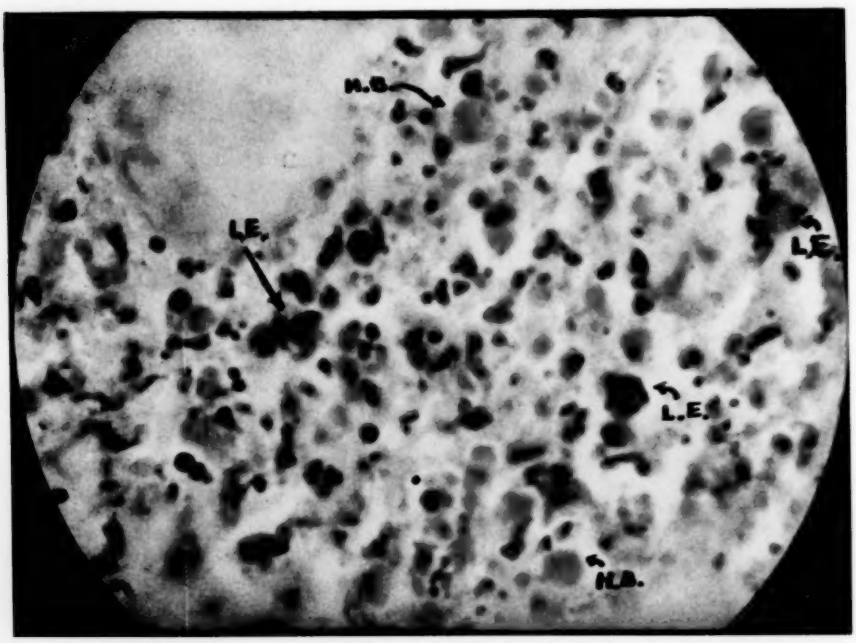

Fig. 4.—Microsection of skin biopsy showing multiple hematoxylin bodies (H.B.) and L.E. cells (L.E.) × 970.

was able to get up with no apparent weakness. The leukocyte count rose to 5,700 per c.mm.; the hematocrit to 33% and the hemoglobin to 10.3 gm.%. A red blood cell survival time started 19 days following steroid initiation was normal. Fluid retention that occurred with steroid therapy caused the anetoderma lesions to balloon markedly (Fig. 5) and Cushingoid features appeared on treatment. Fluid retention was controlled by the use of diuretics and substituting triamcinolone for Prednisone. While the patient improved considerably, at no time did she appear well. The latter part of her course was complicated by thrombocytopenia, resulting in a positive Rumpel-Leede sign, stools positive for blood, and a platelet count of 40,000 per c.mm.; and by a urinary tract infection and nephritis which was substantiated by an Addis count of 4.3 gm. of protein, 43 million leukocytes, and 2 million erythrocytes and a urine culture showing *E. coli*. The cholesterol at this time was 252 mg. per 100 ml. The total protein ranged from the initial 7 gm.% to 5.2 and 6 gm.%. On treatment the globulin ranged from 1.4 gm.% to 2.8 gm.%. The albumin increased to 3.6 gm.%. The blood urea nitrogen rose to 49 and the hematocrit declined to 19% following its initial rise. The leukocyte count decreased again to 2800 per c.mm.

A paronychia developed on the left third digit on May 27, 1959. This was followed by a fever of 105° F. Blood culture at that time grew *Staphlococcus aureus hemolyticus*, coagulase positive. From this point the course was one of rapid, progressive deterioration with the development of grand mal seizures, a stiff neck, and bloody spinal fluid. Following repeated seizures, the patient expired on May 29, 1959.

Postmortem examination revealed recent

massive hemorrhage in the left striate body of the brain with penetration into the left lateral ventricle and general brain edema. Petechial hemorrhages were present in the trachea and bronchi. A bilateral hydrothorax was present with 150 ml. on each side and fibrous pleural adhesions were noted between the right upper and the left lower lobes and the parietal pleura. Early bronchopneumonia was present in several lobes. A hydropericardium of 150 ml. was present. Four vegetations were present on the mitral valve, the largest of which was located at the junction of the anterior and posterior leaflets. At the posterior commissure this measured 0.7 by 0.5 by 0.5 cm. The vegetations were yellow-white, friable, granular and adherent. Culture of the mitral valve grew *Staphlococcus aureus hemolyticus*, coagulase positive. Serial sections of the myocardium showed multiple subepicardial areas of scarring, most marked on the posterior wall. No amyloid was present. The liver was somewhat enlarged and fatty. The spleen showed several areas of scarring similar to scars of old infarcts.

Fig. 5.—Ballooning of anetoderma lesions.

Microscopic sections of the lungs revealed the alveoli coalesced and collapsed. Many of the alveolar lumen were filled with pigment laden macrophages. In other areas there was a pneumonia showing red cells and neutrophils within the alveoli. Purulent bronchiolitis was evident. There were intimal inflammatory changes of the arterioles.

Microscopic sections of the heart showed

the mitral valve with vegetations on the valve surface. The vegetations consisted of masses of bacteria, necrotic cells and fibrinous material. The valve showed thickening and hyalinization. The hyalinized material was more evident at the periphery. The valve itself was thickened and fibrotic. There were blue staining bodies present in the base of the mitral valve. The myocardium showed degeneration and vacuolization of fibers, loss of striations and nuclei. There was a distinct round cell and neutrophilic infiltration together with interstitial fibrosis and hyalinization. There was a distinct focal myocarditis with several smaller areas of active necrosis.

Microscopic sections of the spleen revealed a thickened capsule with hyperemia and fibrous thickening together with iron calcium incrustation of the subcapsular portion of the spleen. There was fibrous adventitial proliferation of the arterioles. The sinusoids were dilated and congested and contained scattered neutrophils and round cells. There was some hyperplasia of the sinusoids, and lymphoid follicles were of moderate size. The arterioles and arteries showed fibrous adventitial proliferation and intimal narrowing. There were multinuclear giant cells and foci of hematopoiesis. Another section of the spleen revealed an organized infarct. The arteries in the vicinity of the infarct showed marked intimal proliferation, narrowing and complete occlusion of the arterial lumen.

Microscopic sections of the liver revealed slight fatty change and congestion of the central zone of the lobules. There was thickening of the periportal areas with slight interstitial infiltration particularly with round cells.

Microscopic sections of the adrenal gland revealed a good amount of lipoid and nodular hyperplasia. In one area there was a focal hemorrhage and in another area there was a distinct focus of necrosis. This was characterized by an infiltration of round cells and neutrophils together with blue staining bodies of various sizes. There was hyalinization and necrosis of the small arterioles of the adrenal.

Microscopic sections of the kidneys revealed distinct subcapsular hemorrhage into the cortex. The glomeruli were present in good numbers and showed moderate thickening of the capsule with some fibrous proliferation and occasional crescent formation. The glomerular tufts showed increase in fibrous tissue, thickening of the capillary walls by hyalin material, and definite hyalin thrombi. There were adhesions of the tuft walls in places. The tubules showed distinct vacuolization of the epithelium. There was interstitial scarring and round cell infiltration. The arteries showed moderate thickening with a few almost entirely occluded by intimal fibrous proliferation. In other areas there were subcapsular necrosis and round cell and neutrophil infiltration. The tubules in other areas were dilated and there was loss of nuclei and cell detail. Within the arteries there was a moderate amount of hyalin seen within the intima.

Microscopic sections of the skin and muscles showed hyperkeratoses, parakeratosis, round cell infiltration of the corium and an infiltration of round cells about the small blood vessels together with loss of skin appendages. Skeletal muscle revealed infiltrations around blood vessels and nerves with round cells.

CASE 2. M.E., age 35, was first admitted to the Edward J. Meyer Memorial Hospital on August 30, 1956, with a chief complaint of severe pain in the right thigh. She was referred to this hospital by her local physician with a diagnosis of dermatomyositis. Her recent past history revealed that she had been well until June, 1956, when she experienced severe pain and spasms of the right intercostal muscles. The right arm then become involved with a constant dull aching pain associated with swelling and spasm. Subsequent to this she developed severe pain in her right thigh. There had been intermittent spasm of the right sternocleidomastoid muscle for a period of 3 years prior to her admission. One year prior to admission both feet and ankles had been red and swollen and had been associated with pain on motion. She was placed on cortisone for a period of one week at that time.

Physical examination was negative except for weakness of the muscles of the right leg with no atrophy. There was partial foot drop of the right foot. Vibratory and position sense, pain, and touch, together with the deep tendon reflexes, were all normal. The mucosa of the mouth showed small red petechial lesions which disappeared within several days of her admission and the skin of the right arm and left hand and right foot showed small raised red nodules which lasted about one week. The remainder of the physical examination was normal.

The patient ran a low-grade fever frequently reaching 100.2° in the afternoons. Her laboratory work revealed a hematocrit of 40 mm., total white blood cell count 7,100 per c.mm., with 51% segmented polymorphonuclear leukocytes, 3% band forms, 2% eosinophils, and 44% lymphocytes. The total serum protein was 6.1 gm.% with 4 gm.% albumin, 2.2 gm.% globulin. The fasting blood sugar

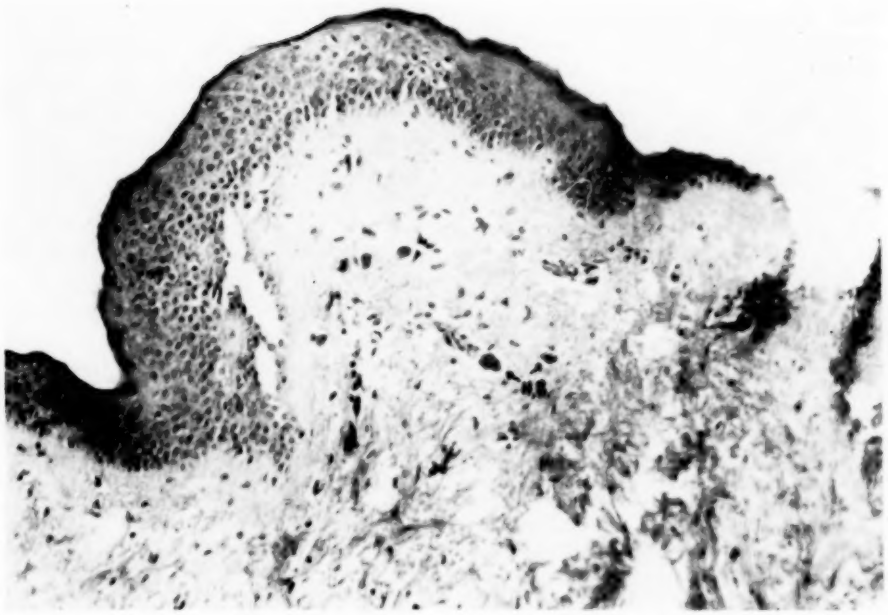

Fig. 6.—Low power magnification of skin biopsy of patient M.E. showing numerous hematoxylin bodies (H.B.) × 120.

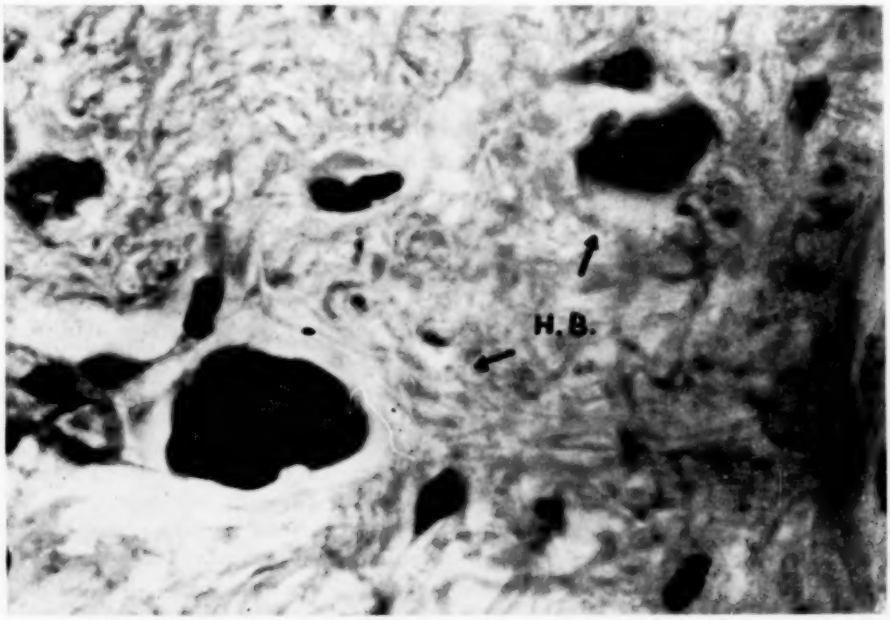

Fig. 7.—× 1000 magnification of hematoxylin bodies of superficial dermis.

was 56 mg. per 100 ml., the blood urea nitrogen 8 mg. per 100 ml., the CO_2-combining power 22 mEq. per L., the serum calcium 10.6 mg. per 100 ml., phosphorus 3.6 mg. per 100 ml. alkaline phosphatase 1.6 mM., cholesterol 281 mg. per 100 ml., and creatinine .7 gm. 24 hour excretion in the urine, creatine .06 gm. 24 hour excretion in the urine. Urinalysis was negative on repeated examinations. Roentgen examination of the chest showed the heart and lungs to be within normal limits. The electrocardiogram was normal. Roentgenographic studies of the cervical spine, pelvis, both shoulders and ankles showed evidence of paravertebral muscle spasm causing slight scoliosis of the dorsal spine. No definite bone or joint pathology was seen. There was minimal osteophytic lipping of the mid-dorsal spine. It was felt that the patient had either dermatomyositis or disseminated lupus. Skin and muscle biopsy were reported as normal except for a minimal perivascular infiltration of round cells in the subcutaneous tissue beneath the skin.

On February 20, 1957, following complaints of spasm and pain in the deltoid area, a skin biopsy was performed (Figs. 6 and 7) which showed the presence of numerous hematoxylin bodies in the superficial dermis. These ranged in size from approximately 10 to 33 microns. The epidermis showed a fairly generalized atrophy with flattening or absence of the rete pegs. There was a peculiar hyalinized thickened subepidermal zone of collagen. No liquefaction degeneration or inflammatory infiltrate could be seen. The findings of hematoxylin bodies and dysplasia of collagen was consistent with the diagnosis of lupus erythematosus disseminatus. The patient was placed on Meticorten 15 mg. a day which was increased to 20 mg. daily. Her course included 2 other admissions to the Edward J. Meyer Memorial Hospital for similar symptoms as those precipitating her prior admission. During this time adjustment of her corticosteroid dosage resulted in complete relief of symptoms and regression of the spleen which had become palpable on each occasion. She was gradually tapered from Meticorten in August of 1957 and since this time has been asymptomatic and completely without re-exacerbation of her disease.

Discussion. To our knowledge, the first case (D.D.) represents the first report of the L.E. cell occurring in the natural cutaneous lesions of S.L.E. The case possesses sufficient criteria and evidence to warrant a diagnosis of systemic lupus erythematosus. The occurrence of L.E. cells in the base of a naturally occurring crusted bullous lesion is not at variance with the commonly accepted theory of the L.E. phenomenon. The phenomenon requires the presence of the L.E. factor, a substance shown to be human 7S gamma globulin (Holman and Deicher[10]), nuclear material from either mature neutrophils or lymphocytes and active phagocytic polymorphonuclear neutrophils. It is not unreasonable to assume the presence of all three in the crusted bullous or vesicular lesion of S.L.E. Incubation which appears to be necessary to produce the L.E. cell *in vitro* could occur in the lesions as it did in the experimentally produced blisters (Watson, O'Leary and Hargraves[22]).

It has been shown by cytochemical means that DNA is an important constituent of the hematoxylin body and of the L.E. mass (Godman, Dietch and Klemperer[5]). DNA was shown to be not depolymerized as was once thought, but instead was found to be associated with an additional protein which is apparently bound to or competing with DNA by the protein's basic groups for the stains used to demonstrate DNA such as methyl green (Godman, Dietch and Klemperer[5]). Using the fluorescent antibody technique Mellors, Ortega and Holman[14] and Friou[4] have shown that the serum from patients with S.L.E. contains L.E. factor or factors which have a marked affinity for nuclei. By digestion of the L.E. factor-nucleoprotein complex by deoxyribnuclease followed by liberation by elution from the digestion residue, the L.E. factor has been isolated from its combination with nucleoprotein. This factor has been found to have the immunological and physical properties of human 7S gamma globulin (Holman and Deicher[10]). This globulin (L.E. factor) in the presence of histone and

deoxyribonucleic acid reacts with the deoxyribonucleo-protein of the cell nucleus as the primary step in the formation of the L.E. cell (Holman and Deicher[10]). It is unable to react with pure DNA. In addition to DNA and histone of the nucleoprotein being necessary for reaction with L.E. cell factor, it appears that probably the specific combining configuration present in the nucleoprotein of the nuclei is necessary for the reaction since reconstructed nucleoprotein is not nearly as effective in absorption of L.E. factor.

There is evidence to support the concept that the antinuclear factors can not enter normal cells *in vivo* (Holman, Deicher and Kunkel[11]). The importance of the antinuclear factors is unknown. The *in vivo* finding of the hematoxylin body and now of L.E. cells suggests that one or more of these factors may play a more significant pathogenic role in S.L.E. than has been assigned to them. It is interesting that fresh frozen percutaneous renal biopsy specimens when stained with antihuman globulin tagged with fluorescein showed a patchy fluorescence in the glomerular capillary wall in 7 of 8 patients with S.L.E. and histologic evidence of lupus nephritis (Freedman, Peters and Kark[3]). This was absent in one patient on 60 mg. of Prednisone.

Bodies meeting the criteria for the diagnosis of hematoxylin bodies were found in the same skin lesions in which L.E. cells were demonstrated and were also found in the biopsy of a lesion in a second case. This finding reaffirms the opinion of Worthington, Baggenstoss and Hargraves[23] and the findings of Muehrcke and Kark *et al.*[15] in kidney biopsy specimens of patients with lupus nephritis that the hematoxylin body is an *in vivo* phenomenon.

Summary. This paper reports the occurrence of L.E. cells and hematoxylin bodies in the naturally occurring skin lesions of S.L.E. L.E. cell formation has been regarded as an *in vitro* phenomenon. L.E. cells have, however, been seen in certain *in vivo* situations. There are objections to considering certain of these as true *in vivo* situations. Hematoxylin bodies, in groups, are highly specific for the postmortem diagnosis of S.L.E. They are considered an *in vivo* phenomenon. L.E. factor or factors are probably responsible for the production of both.

Regardless of whether the L.E. cell is considered as occurring *in vitro* alone or both *in vitro* and *in vivo*, its occurrence in the natural lesions of S.L.E. has not been reported. Their occurrence in the base of a natural blister of S.L.E. is not unexpected as they have been found in experimental blisters in cases of S.L.E. All necessary conditions: L.E. factor, active phagocytic polymorphonuclear granulocytes, nuclear material, and incubation time are present in both situations.

The antinuclear factors are thought not to enter normal cells *in vivo* and their importance is questioned. The *in vivo* findings of the hematoxylin body, and now of the L.E. cell, plus the demonstration of fluorescence in the glomerular capillary wall in fresh frozen kidney specimens of lupus nephritis, stained with fluorescein tagged antihuman globulin, suggests that one or more of these factors may be important in the pathogenesis of S.L.E.

ACKNOWLEDGMENT: We wish to extend our appreciation to Dr. Richard Brown and Mr. Sheldon Dukoff for the photography.

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SUMMARIO IN INTERLINGUA

Le Occurrentia de Cellulas L.E. e de Corpores de Hematoxylina in le Naturalmente Occurrente Lesiones Cutanee de Systemic Lupus Erythematose

Iste communication reporta le identification de cellulas L.E. e de corpores de hematoxylina in le naturalmente occurrente lesiones cutanee de systemic lupus erythematose. On ha reguardate le formation de cellulas L.E. como un phenomeno in vitro. Tamen, cellulas L.E. ha essite vidite in certe situationes in vivo. Il es possibile sublevar objectiones contra considerar certes de ille situationes como vermente situationes in vivo. Corpores de hematoxylina, in gruppos, es altemente specific pro le diagnose post morte de systemic lupus erythematose. Illos es considerate como un phenomeno in vivo. Un factor o plure factores L.E. es probabilemente responsabile pro le production de ambes.

Si o non on considera le cellula L.E. como occurrente solmente in vitro o tanto in vitro como etiam in vivo su occurrentia in le lesiones natural de systemic lupus erythematose ha non previemente essite reportate. Le occurrentia de cellulas L.E. al base de un vesica natural de systemic lupus erythematose non es inexpectate, proque illos occurre cognoscitemente in vesicas experimental de systemic lupus erythematose. Omne le requirite conditiones—factor L.E., activemente phagocytic granulocytos polymorphonucleari, material nucleari, e tempore pro le incubation—es satisfacite equalmente in le duo situationes.

Es opinate que le factores antinucleari non entra in cellulas normal in vivo. Lor importantia es questionabile. Le constatation del occurrentia in vivo de corpores de hematoxylina e nunc etiam de cellulas L.E.–insimul con le demonstration de fluorescentia in le pariete glomerulo-capillar in frescamente congelate specimens renal ab patientes con nephritis lupose e tincturate con globulina antihuman marcate con fluorescina–suggere que un o plures de ille factores es possibilemente importante in le pathogenese de systemic lupus erythematose.

SUMMARIO IN INTERLINGUA

(See page 59 for original article)

Effectos de Exercitio e Isoproterenol Super le Libere Acidos Grasse e Hydratos de Carbon in Patientes Cardiac

1. Le concentrationes arterial e venos de libere acidos grasse (LAG) esseva studiate ante e durante exercitios de gamba o durante le administration intravenose de isoproterenol in un gruppo de 20 patientes cardiac. In 15 casos, etiam le concentration arterial de glucosa, lactato, e pyruvato esseva mesurate.

2. Le exercitio de gamba augmentava le metabolismo aerobie e anaerobie e reduceva in un mesura significative in le concentrationes arterial e iliofemorovenose de LAG. Augmentos del absorption pareva esser indicate per un alteration del differentias arterio-venose. Glucosa parenteral reduceva le nivellos de LAG e augmentava le excesso del production de lactato sub effortio physic in un del patientes.

3. Isoproterenol augmentava marcatemente le nivellos de LAG e le rendimento cardiac sin alterar significativemente le metabolismo del corpore total.

GRANULOCYTOPENIA DUE TO CHLORPROMAZINE: A REPORT OF 11 CASES

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The occurrence of granulocytopenia as a complication of therapy with chlorpromazine (Thorazine) has been well established in the literature (Bernhard *et al.*[1], Boleman[3], Bora and Kline[4], Brandon[5], Council on Pharmacy and Chemistry[6], Emerson and Steinbeck[8], Forman and Ide[9], Giles and Vereker[10], Goldman[11], Hodges and La Zerte[12], Johnson[14], Korst[15], Lomas[17], Moyer[20], Pisciotta *et al.*[22], Platzer and Glaser[23], Pollock[24], Prokopowyz[25], Raskin[26], Roebuck[27], Rosenthal and O'Donnell[28], Rotstein, Frick and Schield[29], Schick and Vicks[30], Tasker[32], Thiriault[33], Tuteur, Kent and Stiller[34], Vetne[35], Weissman and Margolis[38], Yules and Baker[39], Zelman[40]). The frequency of this complication has been difficult to establish and reports of its incidence have varied (Forman and Ide[9], Goldman[11], Rotstein, Frick and Schield[29], Schick and Vicks[30], Council on Pharmacy and Chemistry[6]). We will not attempt to establish the frequency of this complication nor to total the cases in the world literature. We wish simply to record 11 additional cases occurring in a large state mental hospital, and our clinical and therapeutic experiences with these cases.

Case Reports. CASE 1. M.McG., a 61-year-old white woman, a manic depressive, was first given chlorpromazine on August 2, 1955. Over the next 49 days she received a total of 29.5 gm., the highest daily dose being 800 mg. On day 47 of therapy, the patient complained of weakness, nausea, mild diarrhea, headache and cough. Rectal temperature was 103.8° F. Physical examination showed rales at the base of the left lung and the patient was thought to have pneumonitis. Her white blood cell count was 1,050 per c.mm. All cells seen on the peripheral smear were lymphocytes.

Therapy consisted of aqueous penicillin, 500,000 units every fourth hour, streptomycin 0.5 gm. b.i.d., spiromycin 1.0 gm. every sixth hour, probenecid 0.5 gm. every sixth hour, cortisone 100 mg. every sixth hour and gamma globulin 20 ml. intramuscularly. On day 2 of therapy 7 ml. of leukocytic cream was given into each buttock. This dose was repeated on day 4 of therapy. Aqueous penicillin was increased to 1,000,000 units every second hour and streptomycin 0.5 gm. every eighth hour. Gamma globulin 5 ml. into each buttock was repeated on the fourth day of disease. On September 23, day 4 of therapy, the patient developed atrial fibrillation. She was digitalized with 1.2 mg. cedilanid intravenously.

The patient continued a rectal temperature between 101 and 103° F. She expired on September 24, four days after treatment was begun.

Bone marrow biopsy performed September 22, three days after therapy was begun, showed marked depression of granulocytic production. A necropsy revealed edema and congestion of the lungs; fatty metamorphosis of the liver; and bone marrow changes of agranulocytosis.

CASE 2. D.S., a 24-year-old white man with idiopathic mental deficiency, was started on chlorpromazine on October 24, 1955, because he was noisy, would occasionally break

windows and was generally unmanageable. Over the next 51 days he received 18.6 gm. chlorpromazine, the highest daily dose being 400 mg. On day 51 of therapy the patient vomited and complained of abdominal pain. Rectal temperature was 103° F. Examination revealed an injected pharynx, a dry tongue and enlarged tender anterior cervical nodes. The deep tendon reflexes were depressed and there was a bilateral extensor plantar response. White blood cell count was 200 per c.mm., all lymphocytes.

Therapy consisted of 500,000 units of aqueous penicillin followed by 250,000 units every 8 hours; 1 gm. streptomycin b.i.d., cortisone 50 mg. intramuscularly every 6 hours, and parenteral glucose with vitamins. On day 2 of therapy the penicillin was increased to 1 million units every 6 hours and 500 ml. of fresh whole blood were given intravenously.

The patient's neck became massively enlarged and tender. His lips were edematous and the patient experienced marked difficulty in swallowing. On day 3 of therapy, Mysteclin 500,000 units q.i.d. was started orally. An additional 500 ml. blood transfusion was given. Four days after the beginning of therapy the white blood cell count was 4,500 per c.mm. with 60% polymorphonuclear leukocytes. At this time the neck swelling had decreased, lymph nodes were readily distinguished from the soft tissues of the neck and the patient had less difficulty in swallowing and talking. Seven days after the onset of the granulocytopenia all therapy was stopped.

Three weeks after the patient's recovery he was readmitted because of enlarged, tender anterior cervical nodes. At this time the white blood cell count was 7,900 per c.mm. with 71% polymorphonuclears. He responded to penicillin therapy without further complication.

Bone marrow biopsy for granulocytopenia on day 3 of therapy showed maturation arrest of the granulocytic series consistent with agranulocytosis.

CASE 3. E.R., a 58-year-old white woman with mental deficiency was first given chlorpromazine on November 22, 1955. During a period of 46 days she received a total of 9 gm. with the highest daily dose being 200 mg. On day 46 of therapy the drug was stopped because of aggravation of skin eruption. Five days after therapy was discontinued the patient complained of sore throat and difficulty in swallowing. A rectal temperature of 103.6° F. was recorded. White blood cell count was 200 per c.mm. Only lymphocytes could be seen on the peripheral smear.

The patient was treated with oral cortisone 50 mg. every 4 hours, aqueous penicillin 500,000 units every 3 hours, tetracycline 250 mg. every 4 hours. Later the penicillin was increased to 1 million units every 4 hours. Parenteral fluids with vitamins were given. On day 2 of therapy 1,000 ml. of whole blood were given. An additional 500 ml. of whole blood were given on day 3 of therapy. After 5 days of therapy the white blood cell count was 6,300 per c.mm. with 90% lymphocytes and 10% polymorphonuclear leukocytes. Steroids were gradually decreased after a total of 18 days. The patient made a complete recovery and was returned to her psychiatric care.

Bone marrow biopsy one day after therapy for granulocytopenia was begun showed marked reduction in myeloid elements and a maturation arrest of the white cells in the myeloblastic stage.

Bone marrow biopsy repeated 10 days later showed large numbers of myeloid elements resulting in a myeloid-erythroid ratio of 6:1. There were no abnormal cells seen. The red cell series was normal.

CASE 4. G.F., 33-year-old white woman with a schizo-affective psychosis was started on promazine therapy on June 5, 1956. During a period of 28 days she received a total dosage of the 12.6 gm. The maximum daily dose was 800 mg. While she was still receiving promazine, chlorpromazine was started concomitantly on June 26 and continued for 11 days. The patient received a total of 4.4 gm. with a maximum daily dosage of 700 mg. While still on the chlorpromazine therapy, and after promazine had been stopped, the patient spontaneously aborted a 5-month fetus. During treatment for the abortion it was noted that the patient had an inflamed posterior pharynx with mucopurulent discharge. She then was given 6 doses of Ergotrate gr. 1/320th after evacuation of the uterus. The first day after her abortion the patient's white blood cell count was 2,900 per c.mm. with 49% polymorphonuclears and 50% lymphocytes. Chlorpromazine was discontinued, procaine penicillin 600,000 units b.i.d. was started, cortisone 50 mg. every 6 hours and parenteral vitamins were administered. Two days after the abortion the white blood cell count was 1,650 per c.mm. with 6 polymorphonuclears and 94 lymphocytes. The patient was given 500 ml. whole blood and tetracycline 250 mg. q.i.d. was added to the above program. Penicillin was changed to aqueous penicillin and increased to 500,000 units every 6 hours. On day 9 of therapy for the granulocytopenia the white blood cell count was 3,250 per c.mm. Anti-

biotics were discontinued and steroids were gradually decreased.

Bone marrow aspiration done 3 days after the diagnosis of granulocytopenia showed great reduction in myeloid elements and no mature granular white cells.

Liver studies during the period of granulocytopenia were: Bilirubin 0.89 mg. per 100 ml. (0.53 mg. per 100 ml. one minute); alkaline phosphatase 8.68 Shinowara units; serum glutamic oxalacetic transaminase 33.5 units. The patient recovered and returned to psychiatric care.

CASE 5. E.G., 62-year-old white woman with organic psychosis secondary to intracranial infection was first given chlorpromazine on March 5, 1956. Over a period of 153 days she received 35.2 gm. The drug was discontinued on August 10. Chlorpromazine was re-instituted on December 25, because of difficulty in management. Over the next 32 days she received 16.6 gm. with the highest daily dose of 800 mg. daily. Thirty-two days after the second course of therapy was begun she suddenly became weak and her rectal temperature rose to 102° F. Her white blood cell count was 2,400 per c.mm. with 46 lymphocytes and 4 polymorphonuclears in a 50 cell differential count. Examination showed inflammation of the posterior pharyngeal wall with purulent exudate on the tonsillar fossa.

The following therapy was instituted: aqueous penicillin 500,000 units every 6 hours; tetracycline 250 mg. every 6 hours and prednisone 25 mg. daily. The patient was given whole blood transfusion and parenteral fluids. Rectal temperature ranged between 102° and 103° F. The patient expired on January 29, 1957, four days after therapy was instituted. No necropsy was performed.

Bone marrow biopsy performed the first day after therapy was started showed practically complete absence of granulocytes; an occasional blast was seen.

CASE 6. S.S., 57-year-old white woman, a paranoid schizophrenic, was first given chlorpromazine on December 12, 1956. Over a period of 56 days she received a total of 36.6 gm., the highest daily dose being 1.0 gm. On day 56 of therapy (February 5, 1957) the patient accidentally fell. Since she had been unsteady on her feet, chlorpromazine was discontinued. The next day the patient's rectal temperature was 104° F. She complained of sore throat and weakness. A white blood cell count showed 2,400 per c.mm. with 40% polymorphonuclears and 60% lymphocytes.

The following therapy was begun: Aqueous penicillin 500,000 units every 6 hours; streptomycin 0.5 gm. every 12 hours; prednisone 25 mg. every 6 hours; tetracycline 0.5 gm. every 6 hours and parenteral glucose with vitamins. Five hundred milliliters of whole blood were given on each of the first 2 days of therapy. Despite this program, the patient maintained a spiking temperature to 106° F. and became stuporous. The white count dropped to 850 cells per c.mm., all cells identified were lymphocytes. She expired on February 13, seven days after therapy for granulocytopenia was started.

Bone marrow biopsy done one day after therapy was instituted showed complete absence of myelocytes and mature granular white blood cells.

Her liver tests showed: Bilirubin 1.85 mg. per 100 ml. (1 minute 0.77 mg. per 100 ml.); cephalin flocculation 3+; thymol flocculation 0; thymol turbidity 1.54 units; zinc turbidity 11.16 units; alkaline phosphatase 2.64 Shinowara units; cholesterol 165 mg. per 100 ml. and serum glutamic-oxalacetic transaminase 84 units. Necropsy revealed: Massive hemorrhage into the bases of both lungs; hemorrhage into both adrenals; acute lymphadenitis of the mesenteric lymph nodes; acute stomatitis; and acute esophagitis.

CASE 7. C.S., 60-year-old white woman, a schizophrenic, was started on chlorpromazine therapy on July 30, 1957. Over a period of 43 days she received a total of 4.3 gm. with the highest daily dose being 100 mg. On day 43 of therapy she complained of sore throat and fever and chlorpromazine was discontinued. Penicillin and streptomycin were started. On the following day her throat was inflamed and suggested granulocytopenia. White blood cell count was 1000 per c.mm., of 50 white cells counted, all were lymphocytes.

The following regimen was instituted: Aqueous penicillin 500,000 units every 6 hours, streptomycin 0.5 gm. b.i.d., prednisone 25 mg. four times daily and tetracycline 250 mg. every 6 hours. The patient also received daily parenteral glucose and vitamins with 500 mg. chlortetracycline in each 1000 ml. of glucose solution. During the first 3 days of treatment 1500 ml. of whole blood were given. On day 4 of therapy 10 ml. of gamma globulin were given. On day 5 of therapy the patient was afebrile and by day 13 all medications had been stopped. Leukocyte count was 9,200 per c.mm. with a normal differential count. Patient recovered.

Bone marrow biopsy performed on day 1 of therapy showed normal erythrocyte development and platelet development. There was

almost complete absence of cells of the granulocytic series. Studies revealed: Bilirubin total 1.15 mg. per 100 ml. (1 minute 0.5 mg. per 100 ml.); cephalin flocculation 2+; thymol flocculation 0; thymol turbidity 2.36 units and zinc turbidity 9.68 units; and alkaline phosphatase 7.30.

CASE 8. C.B., 56-year-old white woman, a schizophrenic, was started on chlorpromazine on March 3, 1957. During the next 383 days she received a total dose of 327.1 gm. chlorpromazine. During this interval her highest daily dose was 1.0 gm. Between the dates of April 17, 1957, and January 17, 1958, the patient received Cogentin by mouth because of the development of drug-induced Parkinsonism.

On March 6, 1958, the 368th day of chlorpromazine therapy, the patient first appeared to be acutely ill. Since a number of other patients in her building were at that time suffering from influenza-like symptoms her initial treatment consisted merely of bed rest and simple symptomatic measures. She showed improvement in approximately 96 hours but 3 days later relapsed and again had to be confined to her bed with loose stools, nausea, dizziness, weakness and a slight temperature elevation. Again her temperature subsided and her complaints disappeared after 3 days of bed rest. On March 22, when patient had loose stools containing some blood, chlorpromazine therapy was discontinued. A white blood cell count at the time of her admission showed 1400 cells per c.mm. No polymorphonuclear cells seen in a 50 cell differential.

Therapy consisted of: Tetracycline 250 mg. every 6 hours, aqueous penicillin 500,000 units every 4 hours, streptomycin 1 gm. every 12 hours, prednisone 20 mg. q.i.d. Twenty-four hours later she also received gamma globulin. Fresh whole blood, in a total amount of 1500 ml., was given for 3 days.

Liver studies showed evidence of liver damage and the following day clinical icterus was apparent. During the next 4 days she became more intensely jaundiced and genital ulceration was noted. Her total bilirubin rose to 43.4 mg. per 100 ml. and her white blood cell count fell to 300 cells per c.mm. No cells of the myeloid series were seen. She deteriorated rapidly during the next 12 hours and expired on March 31, 1958.

A bone marrow biopsy performed on March 25 and reported postmortem showed the marrow so diluted with peripheral blood that an accurate interpretation was difficult. No cells of the myelocytic series, however, could be identified in the smears of the marrow aspirate. Necropsy revealed: hepatitis of the Thorazine type; necrosis of the adrenals; bone marrow changes of granulocytopenia.

CASE 9. C.J.S., 46-year-old white man, a schizophrenic, was placed on chlorpromazine on June 2, 1958, and over a period of 54 days received 33 gm. with a maximum daily dosage of 800 mg.

On day 54 of therapy the patient complained of a sore throat. Examination revealed purulent and beefy red throat and a rectal temperature of 105° F. White blood cell count showed 950 leukocytes per c.mm., all lymphocytes.

Laboratory studies the day following admission showed: Total bilirubin 3.04 mg. per 100 ml. (1 minute 0.68 mg. per 100 ml.); cephalin flocculation 0; thymol flocculation 0; thymol turbidity 3.01; zinc turbidity 8.12; alkaline phosphatase 1.65 Shinowara units; serum glutamic-oxalacetic transaminase 73 units; total protein 6.9 gm.%; albumin 4.7 gm.% and globulin 2.2 gm.%.

The following therapy was instituted: Aqueous penicillin 300,000 units every 4 hours, streptomycin 0.5 gm. b.i.d., prednisone 15 mg. t.i.d., tetracycline 250 mg. every 6 hours. The patient also was given parenteral fluids, and 3 transfusions of 500 ml. whole blood each. Serial white blood cell counts first showed the appearance of granulocytes 11 days after therapy. Final count at time of clinical recovery was 10,500 per c.mm. with a differential of 77% polymorphonuclear cells.

Bone marrow biopsy was done the day following admission. The specimen consisted almost entirely of peripheral blood. However, it was notable that there were no granulocytes which tends to confirm the diagnosis of agranulocytosis.

CASE 10. H.S., 64-year-old white woman, a schizophrenic, was started on chlorpromazine on December 13, 1958. Over the next 70 days she received 28 gm., the highest daily dose being 400 mg. On day 70 of therapy she developed fever. Physical examination showed a diffuse hyperemia of the oropharynx and a few inspiratory rales in the left lung field. Blood count revealed a hemoglobin of 11 gm., white blood cell count of 750 per c.mm. No neutrophils were seen on smear. (The patient's last prior white blood cell count had been performed on December 30, 1958, approximately 7 weeks prior to her admission, and had been reported as 6,000 cells per c.mm. with a normal differential count.)

Treatment consisted of bed rest under strict isolation technique. The patient re-

TABLE 1

Patient				Initial WBC	Duration of Drug ℞	Total Dose (gm.)	Maximum Daily Dose (mg.)	Interval Symptom Onset to ℞	Result	Remarks
1. M. McG.	61	F	W	1000 P–0 L–100	49 days	29.5	800	4 days	Died	
2. D. S.	24	M	W	200 P–0 L–100	51 days	18.6	400	24 hrs.	Recovered	
3. E. R.	48	F	W	300 P–0 L–100	46 days	9.0	200	24 hrs.	Recovered	
4.*G. F.	33	F	W	2900–1650 P–49 P–6 L–50 L–94	c 11 days p 28 days	4.4 12.6	700 800	Unknown	Recovered	
5. E. G.	62	F	W	*a.* normal *b.* 1400 P–1† L–39 M–10	153 days 32 days	35.2 16.6	800 800	– 24 hrs.	– Died	Interval between courses was 137 days
6. S. S.	57	F	W	2400 P–40 L–60	56 days	36.6	1000	24 hrs.	Died	
7. C. S.	60	F	W	1000 All lymphs	43 days	4.3	100	48 hrs.	Recovered	
8. C. B.	56	F	W	1400 L–49† M–1	383 days	327.1	1000	48 hrs.	Died	
9. C. J. S.	47	M	W	950 P–0 L–100	54 days	33.0	800	24 hrs.	Recovered	
10. H. S.	64	F	W	750 P–0 L–100	70 days	28.0	400	36 hrs.	Recovered	
11. V. P.	47	F	W	*a.* normal *b.* normal *c.* 1750 P–12† L–38	366 days 124 days 591 days	107.8 34.0 234.0	800 400 800	– – 72 hrs.	– – Recovered	6 mo. interval before second course; 4 mo. interval before third course. (Presented an acute abdomen).

* Case No. 4 was receiving chlorpromazine and promazine concurrently.
† Only 50 cells counted in differential.
P Polymorphonuclear.
L Lymphocyte.
M Monocyte.

ceived penicillin 500,000 units every 6 hours and erythromycin 500 mg. every 6 hours. On the patient's second hospital day the aqueous penicillin and erythromycin were discontinued and she began to receive 600,000 units of procaine penicillin twice daily and streptomycin 0.5 gm. every 12 hours plus oxytetracycline 0.5 gm. every 6 hours. On the same day prednisone was added in doses of 10 mg. q.i.d. Throughout the remainder of the patient's first week the white blood cell count remained between 1,000 and 2,000 cells per c.mm. with no neutrophils seen. The temperature during this time was constantly elevated above 102° F. rectally until the morning of February 28, 1959, her eighth hospital day. That morning she was afebrile and seemed greatly improved. Her white blood cell count was 1,850 per c.mm. No differential count was performed on that day.

Three days later the patient again spiked a temperature of 102.4° F. rectally and began to deteriorate clinically. Her temperature varied from 102 to 106° F. rectally during the next 72 hours and on March 4, 1959, a maculopapular rash most marked over the right scapula and the lumbosacral area was seen. This rash was originally ascribed to a contact dermatitis due to a rubber draw sheet. During the next 48 hours it became more obvious that the patient was having a penicillin reaction. The rash spread to involve much of her body and she began to complain of joint pains. Accordingly, on March 6, 1959, all antibiotics were stopped except chloromycetin which was administered in a dose of 0.5 gm. every 6 hours. The same day the patient received penicillinase (Neutrapen) 800,000 units intramuscularly. In less than 24 hours the rash described had cleared and the patient was afebrile. Her steroids were tapered and discontinued. On the morning of March 10, 1959, 20 days after the onset of her acute illness, her white blood cell count was reported as 22,000 with 80% polymorphonuclear cells.

The patient remained afebrile for the rest of her hospital stay and was discharged with a white blood cell count of 9,250 cells per c.mm. and a normal differential count.

CASE 11. V.P., 47-year-old white woman, a schizophrenic, was admitted to Norristown State Hospital on April 8, 1947. She had 3 prolonged courses of chlorpromazine therapy. In her first course she received 107.8 gm. chlorpromazine over a period of 366 days. Her second course was for 124 days and the total dose of chlorpromazine administered in this period was 34 gm. there was a 6-months' interval between these two courses and the patient manifested no undesirable side effects. Four months after the second course of chlorpromazine the third was started. It lasted 591 days with a total dosage of 234 gm. The maximum daily dose during this period was 800 mg. On day 591 of the third course the patient was seen because of a history of 3 days of lethargy and 24 hours of right lower quadrant pain, nausea and vomiting. Examination was not remarkable except for the presence of localized tenderness and guarding in the right lower quadrant. Her bowel sounds were noted to be hyperactive. The white blood cell count was 1,700 cells per c.mm. Only 50 cells could be counted on the differential smear and of these, 12 were polymorphonuclears. Laboratory studies: Serum bilirubin 1.49 mg. per 100 ml. (0.37 mg. per 100 ml. direct); both cephalin flocculation and thymol flocculation were 4+; thymol turbidity 7.14 units; zinc turbidity 29.5 units; alkaline phosphatase 4.67 Shinowara units; cholesterol 184 mg. per 100 ml., 56% esterified; serum glutamic-oxalacetic transaminase 30 sigma units.

The patient was treated with bed rest, isolation, intravenous fluids, aqueous penicillin 500,000 units every 6 hours, streptomycin 0.5 gm. every 12 hours, and chloramphenicol 0.5 gm. every 6 hours.

During the first week on this regimen the patient's abdominal complaints gradually subsided and the right lower quadrant tenderness and guarding slowly disappeared. The patient did not become afebrile until her thirteenth hospital day. As liver function tests were followed, her bilirubin rose gradually to 1.84 mg. per 100 ml. (0.65 mg. per 100 ml. direct) on the twelfth hospital day. Flocculation tests remained at 4+ and both thymol and zinc turbidity tests remained elevated. Her white blood cell count rose slowly but steadily and by her thirteenth hospital day was 4,100 cells per c.mm. with 50% polymorphonuclears. During the following 2 months the patient's liver flocculation tests remained markedly abnormal. The serum glutamic-oxalacetic transaminase and serum iron levels were repeatedly within normal limits. A cholecystogram performed approximately 6 weeks after the onset of her acute illness revealed a poorly functioning gallbladder with several opaque biliary calculi.

At no time in this patient's course did she manifest subjective or objective evidence of the usual granulocytopenic pharyngitis.

Results. All our cases were observed during the 4-year period from 1956 to

L Lymphocyte.
M Monocyte.

to 1959 inclusive. This period coincides with the peak use of chlorpromazine in this hospital. We believe we have witnessed a decreased incidence recently as other new phenothiazine and non-phenothiazine drugs have come to be used more frequently (See Table 2).

TABLE 2.—CASES DISCOVERED DURING PERIOD OF OBSERVATION

Period	*Cases Discovered*
July 1, 1955 to July 1, 1956	3
July 1, 1956 to July 1, 1957	3
July 1, 1957 to July 1, 1958	2
July 1, 1958 to July 1, 1959	3
July 1, 1959 to July 1, 1960	0

The exact number of patients receiving this agent at any one time is not known to us but we have estimated that at the height of its use, 1000 patients of the 4500 in this institution were receiving it.

AGE. The youngest patient in our series was 24 years old and the oldest 64 years old. Only 4 patients were over 60 years of age.

SEX. There were 9 females and 2 males. The approximate ratio of females to males in hospital population is 1.3:1.

RACE. All 11 patients were Caucasian. The Negro represents 8% of the hospital population.

DOSAGE. The smallest amount of chlorpromazine observed by us to produce granulocytopenia was 4.3 gm. given over a 43 day period (Case 7). The maximum daily dose in this patient had been only 100 mg.

The highest total dose recorded in our cases was 234 gm. administered over a period of 591 days (Case 11). The maximum daily dose in this patient was 800 mg. Cases 8 and 11 are of special interest since both had had prior uncomplicated courses of chlorpromazine (See Table 1).

CLINICAL PICTURE. It will be noted from the case histories that most of our patients presented fever, pharyngitis and prostration. One patient had pneumonitis (Case 1) and one had an acute abdomen (Case 11).

LABORATORY DATA. Six patients had no granulocytes seen in a smear of their peripheral blood at the time diagnosis was established. The lowest white blood cell count was 200 cells per c.mm., and the highest was 2900 cells per c.mm. It required 5 to 20 days for the reappearance of normal total white blood cell counts and differentials in these patients. A transient leukocytosis was frequently observed as improvement occurred.

No instances of thrombocytopenia were seen.

In those 9 cases in which the bone marrow was examined, occasional myeloblasts were seen but otherwise there was a marked paucity of cells of the granulocytic series. No impairment of red cell or platelet formation was noted.

Hepatic function tests were performed in 6 patients. The results were normal in Case 4 and only minimally impaired in Cases 6 and 7. Tests in Case 8 showed more severe damage and were substantiated at necropsy, while Case 9 had only an elevation of serum glutamic-oxalacetic transaminase.

Case 11, however, displayed consistently abnormal flocculation tests and an elevated gamma globulin. Although her serum bilirubin was 6.6 mg. per 100 ml. on admission, it fell rapidly and remained below 2 mg. per 100 ml. for the remainder of the course. Her transaminase was slightly elevated on one occasion (87 sigma units) but her serum iron level was normal. This patient was later demonstrated to have

opaque calculi in her gallbladder and the relative importance of the various strains upon her hepatic function is difficult to assess.

THERAPY. In addition to general supportive care (fluids, diet, vitamins, and the like), the patients were treated under isolation precautions. We have felt this to be an essential part of their management since they were members of a general hospital population and might be exposed to cross-infection. They all received penicillin with streptomycin or tetracyclines, or both. Two cases received chloramphenicol; and erythromycin was used in one patient.

All patients except one (Case 11) received steroids. Cases 1 through 4 received cortisone in doses of 200 mg. to 400 mg. per day, while Cases 5 through 9 were treated with prednisone, 25 to 100 mg. per day.

All cases except 4 and 10 received fresh whole blood.

Cases 1, 7 and 8 were given gamma globulin as well as antibiotics and Case 1 also received leukocytic cream on two occasions.

MORTALITY. We are unable to correlate any specific factor in therapy with survival. Our mortality was 36% (4 of 11 cases).

Correlation of initial white blood cell count with mortality does not seem to be significant. All our deaths occurred in patients whose initial counts were 1000 cells per c.mm. or above, while 2 of our surviving cases had initial white blood cell counts of 200 cells per c.mm., all of which were lymphocytes (Cases 2 and 3).

It has been our experience that although most deaths from granulocytopenia occur in the first 2 weeks, survival beyond this period is no guarantee of recovery, namely, Case 8.

Only 2 of our cases were clinically jaundiced (Cases 8 and 11). Of these, only the former died, the latter surviving with persistent laboratory evidence of hepato-cellular disease.

Discussion. The administration of any drug to patients entails calculated risks which must be weighed against the potential good to be derived from its use. The value of the phenothiazine group of tranquilizing agents in the management of the psychotic patient is undisputed. We would decry any attempt to label this group of agents as too toxic for general use. However, we join with many others in the literature in emphasizing the hazards attendant to their administration. It is of the utmost importance that all physicians using these or other agents be aware of all possible complications, and be prepared to recognize them when they occur.

The use of routine white blood cell counts at stated intervals has frequently been suggested as a safeguard in the patient receiving phenothiazines. While such a procedure may to some extent allay the apprehension of physicians using these agents, it has been repeatedly demonstrated that such a practice gives no absolute assurance that toxic effects will be foreseen. It is mandatory that patients on high dosage or prolonged phenothiazine therapy, or both, be observed closely with daily temperature checks and frequent inspection of the oropharynx. We feel that such "throat rounds" may prove to be the most practical and valuable approach in detecting phenothiazine-induced granulocytopenia. These objective observations are particularly important in the psychotic patient who will not or cannot offer complaints.

Most large institutions will find it impractical to check all parameters of phenothiazine toxicity (white blood cell count, liver profile, and others) at routine intervals. Some form of objective observation of the patient should

supplant or complement such procedures.

It has been observed that the intrahepatic cholestasis due to chlorpromazine is likely to occur in the first 3 weeks of therapy (Schiff[31]). Granulocytopenia, on the other hand, may occur after months of treatment unmarked by any untoward side effects. We have found (as have others) that this complication is usually a later complication (Pisciotta *et al.*[22]). Only 2 of our cases occurred in less than 6 weeks (Cases 4 and 5). Two of our cases occurred after more than one year of continuous therapy (Cases 8 and 11).

The age, sex or race of the patient or a history of a previous uncomplicated course of therapy with these agents, do not justify a lack of vigilance. The incidence of chlorpromazine granulocytopenia in the Negro must be quite low. To our knowledge there has been no report in the American or English literature of such granulocytopenia in the Negro due to chlorpromazine. Lambo records his experiences with chlorpromazine in a large Negro population in Africa[16]. He reports no instance of jaundice, skin rash or granulocytopenia.

Once granulocytopenia has occurred many physicians may be prone to employ all known modalities of treatment because of the critical state of these patients and the high mortality resulting from this complication. Our own therapy in these cases has been quite vigorous but we wish to point out that there is still considerable controversy over the value of steroids as marrow stimulating agents. Some authorities on noting the transient leukocytosis that often follows recovery remark that this has been seen only in steroid-treated patients (Goldman[11]). Careful survey of the literature does not confirm this view and a firm basis for the use of steroids seems to be still lacking (Pisciotta *et al.*[22], Rotstein, Frick and Schield[29]). The role of whole blood in the treatment of these patients is also open to discussion. As a part of good general supportive therapy significant anemias should be corrected. The value of whole blood in terms of provision of extra properdin, complement and such nonspecific defensive agents is not known. The risks attendant to steroid therapy and whole blood transfusion must always be weighed against the advantage in any clinical situation.

The most reasonable approach to drug-induced granulocytopenia is withdrawal of the offending agent, good supportive therapy, and antibiotics aimed at organisms isolated. In the absence of specific cultures, penicillin would seem adequate for the early treatment of the infection accompanying agranulocytosis.

The clinician following a patient with granulocytopenia expects recovery to follow drug withdrawal. However, it must be realized that chlorpromazine is slowly excreted. Evidence of its presence may be found in the urine for as long as 28 days after the drug has been discontinued (Boger[2]). It may be of interest in the future to attempt to correlate renewed myelopoiesis with the disappearance of chlopromazine or its metabolites from the urine.

In terms of prognosis, it would seem that the level of the first or lowest white blood cell count is of no prognostic significance. The absolute number of circulating neutrophils also fails to correlate with mortality. The presence of co-existent disease makes for unfavorable prognosis (Hodges and LaZerte[12]. Pisciotta *et al.*[22]), as does the presence of jaundice (Giles and Vereker[10], Hodges and LaZerte[12], Tasker[32], Thiriault[33]).

Transient monocytosis has been observed with recovery and may indicate reactivation of myelopoiesis (Pisciotta

et al.[22], Rotstein, Frick and Schield[29], Schick and Vicks[30]).

The mechanism by which chlorpromazine produces granulocytopenia is unknown. It does not seem to be depressant to all marrows with a linear dose-response relationship as is seen with such agents as 6-mercaptopurine or triethylene melamine.

The granulocytopenia seen with amidopyrine may be re-induced by minute amounts of the offending agent in persons who have had prior marrow depression from its used (Dameshek and Colmes[7], Madison and Squier[18]). *In vitro* leukagglutinins and leukolysins have been demonstrated in these cases (Moeschlin[19]). With chlorpromazine, on the other hand, while subsequent exposure has produced granulocytopenia, the doses required are well above the minimal range (Pisciotta *et al.*[22], Platzer and Glaser[23], Yules and Baker[39]), and Jacoby has reported uneventful readministration to one patient who had twice developed granulocytopenia at lower dosages (Jacoby[13]). There has been no successful demonstration of leukocyte antibodies in granulocytopenia due to chlorpromazine (Pisciotta *et al.*[22], Rotstein, Frick and Schield[29]).

It may be that the sulfur-containing chlorpromazine molecule is able to enter into metabolic competition with sulfur-containing amino acids in certain individuals, as has been suggested by Pisciotta *et al.*[22]. The importance of such sulfur-bearing amino acids in leukopoiesis, their protective effects upon the nitrogen mustard treated marrow, and their paucity in granulocytopenic marrows have been demonstrated (Parker and Krocke[21], Weisberger and Heinle[36], Weisberger and Levine[37]).

Such a mechanism, invoking the law of mass action, might be used to explain the apparent "threshold" for granulocytopenia eventually exceeded in Case 11 of our series but fails to explain the experience of most others with readministration of chlorpromazine.

Summary. Eleven cases of granulocytopenia due to chlorpromazine therapy are reported. It was found that the duration of therapy and size of dose varied and was not necessarily a factor in the production of granulocytopenia. The clinical picture was characterized by fever, pharyngitis and prostration. Two cases presented with pneumonitis and one with an acute abdomen. Therapy consisted of general supportive measures, antibiotics, steroids and blood. Seven of the 11 cases survived. We were unable to correlate the survival with any specific factor in therapy. The importance of close observation for fever, pharyngitis, and deterioration in the clinical appearance of patients receiving chlorpromazine therapy as a means of early detection of a granulocytopenia is emphasized.

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SUMMARIO IN INTERLINGUA

Granulocytopenia per Causa de Chlorpromazina: Un Reporto de 11 Casos

Es reportate 11 casos de granulocytopenia causate per therapia a chlorpromazina. Esseva notate que le duration del therapia e le fortia del dose variava e non esseva necessarimente un factor in le production de granulocytopenia. Le tableau clinic esseva characterisate per febre, pharyngitis, e prostration. Duo casos presentava pneumonitis. In un tertie, le abdomine esseva afficite. Le therapia consisteva de mesuras generalmente supportative, de antibioticos, de steroides, e de sanguine. Septe del 11 patientes superviveva. Il non esseva possibile correlationar le superviventia con un factor specific in le therapia. Es signalate le importantia de un stricte observation pro febre, pharyngitis, e deterioration del stato clinic in patientes sub therapia a chlorpromazina in le interesse de un detection precoce de granulocytopenia.

URINARY ABNORMALITIES FROM OVER-USE OF MUSCLES

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The aches, stiffness and discomfort which may follow muscular exertion are too well known to require any comment other than the reminder that the chemical and physiological processes involved in their production are largely unknown. In human beings, horses, dogs and doubtless in other animals, over-use of unconditioned large muscle groups may lead not only to the above symptoms, but to actual muscle swelling and tenderness, and in the case of horses, irreversible changes. In both humans and horses, over-use of powerful muscles may also result in proteinuria, cylindruria, hemoglobinuria, myoglobinuria and hematuria, especially following periods of muscular inactivity.* The cause of this phenomenon too remains a mystery, though it has aroused considerable speculation, especially on the part of veterinarians (Hutyra *et al.*[7]). The following case history is typical of the hemoglobinuria which may follow the unwonted use of large muscle groups in man.

Case Report. R. J. W. a male, aged 20, presented himself to the health service of Drexel Institute of Technology on May 12, 1960, complaining that he was passing brown urine. He stated that he had had no previous urinary disturbance, but that on the night of May 10, in the course of fraternity hazing, he was required to do "deep knee bends" squatting to the floor about 150 to 200 times in 20 minutes. He was then put to work scrubbing floors all night and was only allowed to drink one glass of water, though he felt quite thirsty. His thighs were extremely painful and tender from the exercise. On the morning of May 11, after having worked all night except for a 30 minute rest in a chair, he went to a massage parlor where a 15 minute treatment in a "sweat box" caused him to perspire freely. His legs were then "rubbed down" with epsom salts, and he slept for 3 hours. That evening at about 7 p.m. and again at 10:00 p.m. he noticed that his urine was brown in color. There appeared to be no diminution in quantity.

On May 12, at 10:00 a.m. the urine which has been passed 3 hours before was presented for examination and proved to be brown in color and cloudy. Centrifugation produced 1.5 cm. of dark brown sediment which proved to be composed largely of dark granular casts admixed with leukoytes, gave a strongly positive test for occult blood with "hematest" tablets but revealed no erythrocytes on microscopic examination. In the uncentrifuged specimen 432 casts were counted per c.mm. of urine (Fig. 1). Spectroanalysis yielded positive results for hemoglobin, and negative for myoglobin. The blood serum was normal in color, contained 1.1 mg. per 100 ml. of creatinine, and revealed neither hemoglobin nor myoglobin. The patient was ordered to drink 500 ml. of water containing 1 gm. of sodium bicarbonate, and told to save all urine specimens voided for the next 24 hours, to go home, rest and drink an abundance of water. The ensuing samples re-

*In some parts of Europe paralytic hemoglobinuria or myoglobinuria associated with the resumption of work after holidays, has been given the name of Easter disease, Whitsuntide disease or Holiday disease of horses (Hutyra *et al.*[7]).

vealed progressively less protein, progressively lost their brown color and casts, and gave a progressively weaker reaction for hemoglobin. On May 16 the urine was normal in all respects. From first to last no erythrocytes could be identified in the sediment. A repeat serum creatinine 3 weeks later was again normal: 1.2 mg. per 100 ml.

The urines of 7 other men undergoing the same initiation but who were subjected to less rigorous hazing were examined. Two revealed the presence of protein and hemoglobin, one in addition containing an occasional dark granular cast. This youth stated that his urine presented a brownish color on May 11. Even as late as May 17 a trace of protein and an occasional dark granular cast were detected in his urine, which continued to give a faintly positive reaction for hemolgobin until this time.

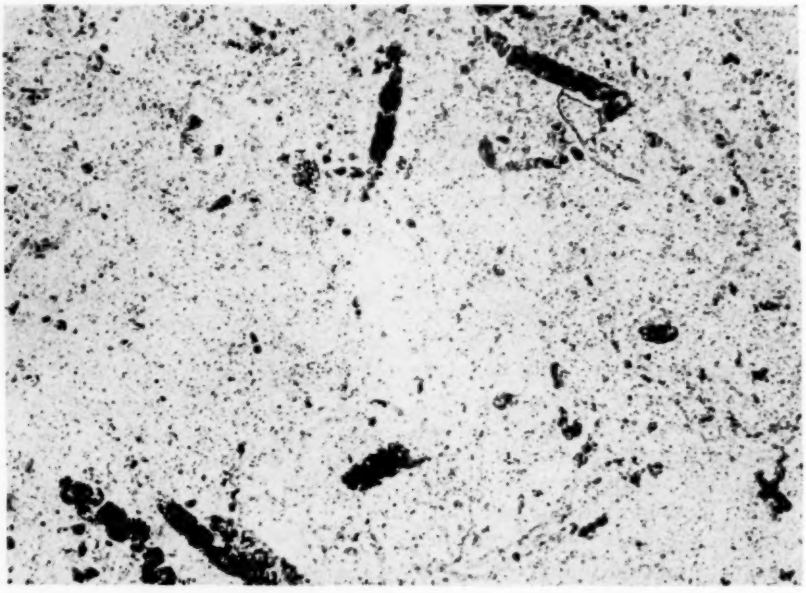

Fig. 1.—Microscopic appearance of urine following muscular over-use. Note abundance of dark granular casts in uncentrifuged specimen.

Discussion. Increased amounts of albumin, casts, and red blood cells were first observed in the urines of athletes 50 years ago (Barach[2]). In recent years interest in this phenomenon has been revived. Gardner[4] pointed out that the urinary sediment changes following participation in football could resemble the sediment found in patients with acute glomerular nephritis, an observation which has subsequently been confirmed (Howenstine[6]).

Alyea and Parish[1] collected urines from young men participating in a variety of sports, and found that these urinary sediment abnormalities were not dependent upon bodily contact for their appearance, for example, swimmers as well as football and lacrosse players developed proteinuria, cylinduria, and hematuria. Their data demonstrated that the urine sediment abnormalities were related to the degree of exertion expended by each individual. These authors also reviewed some

of the mechanisms by which exercise may produce these abnormalities. During exercise the renal plasma flow decreases and endogenous epinephrine is released; both of these factors might result in temporary renal anoxia and consequently lead to the appearance of urinary sediment abnormalities. It has recently been observed in rats that increased amounts of protein in the urine appear when urinary pH falls, an observation that might also be used to explain the proteinuria that accompanies the aciduria following physical exertion (Gardner[5]).

In addition to the physiological changes that accompany exercise, myoglobinuria and hemoglobinuria occasionally can be found in the urines of young athletes. Stahl[8] and Howenstine[6] believe that these urinary sediment changes might be due to the release of myoglobin from the muscle or to the breakdown of red blood cells within muscle substance, or to a combination of the two. These studies were deficient, however, in that the authors failed to determine whether or not hemoglobinemia accompanied the hemoglobinuria in their cases.

The clinical picture of our patient was similar to those of the patients described by Stahl[8] and Howenstine[6]. However, myoglobinuria was not found on spectrophotometric determinations in this individual. In view of the facts that strenuous exercise such as that which was imposed upon our patient is capable of producing proteinuria, cylinduria and hematuria, and that erythrocytes were absent from his urine and hemoglobin from his serum, we conclude that his hemoglobinuria was the result of red cell hemolysis within the urinary tract. The prompt disappearance of all urinary abnormalities, coupled with the lack of other clinical evidence in support of active renal disease, for example, repeatedly normal serum creatinines, led us to believe that no permanent kidney damage had been sustained.

A review of the literature indicates that overzealous participation in unwonted knee-bending exercises offers a fruitful source of material for the study of the phenomena presented by our case. It would be interesting to follow the changes in the serum, urine, electromyograms and renal blood flows, in a group of unconditioned volunteers performing such exercise. The findings might throw light not only on problems of muscle conditioning, but on the enigma of acute glomerulonephritis. We have been unable to find any recorded fatalities associated with the hemoglobinuria or myoglobinuria of athletes, though in horses suffering from hemoglobinuric or myoglobinuric paralysis a mortality rate of between 20 and 70% is reported (Hutyra *et al.*[7]), and fatal paralytic myohemoglobinuria has been reported in man (Bywaters[3]).

Summary. The case is presented of a youth who about 24 hours after performing 150 to 200 "squats" resulting in painful thigh muscles, began passing brown urine loaded with dark granular casts and leukocytes, and giving a strongly positive test for hemoglobin (no erythrocytes were seen). Complete recovery apparently ensued within 5 days. The subject of urinary changes incident to over-use of muscles is discussed.

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SUMMARIO IN INTERLINGUA

Anormalitates Urinari post Effortio Abusive de Musculos

Es presentate le caso de un adolescente le qual—24 horas post executar 150 a 200 "flexiones de gamba" resultante in dolorose musculos femoral—comenciava vacuar urina de color brun cargate de cylindros granular e leucocytos e producente un fortemente positive test pro hemoglobina. Nulle erythrocytos esseva notate. Un restablimento complete se effectuava apparentemente intra 5 dies. Le thema de alterationes urinari post abuso muscular es discutite.

EFFECTS OF EXERCISE AND ISOPROTERENOL ON FREE FATTY ACIDS AND CARBOHYDRATES IN CARDIAC PATIENTS*

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Dole reported in 1956 that the plasma concentration of non-esterified free fatty acids (FFA) increased with either fasting or injections of epinephrine, and diminished with feeding oral glucose or injection of insulin (Dole[7]). Ingestion of corn oil produced a gross lipemia, but failed to change the level of FFA. Immediately after this, Gordon and Cherkes reported similar findings with respect to fasting, glucose and epinephrine, and presented evidence that these fatty acids originated in adipose tissue and were mobilized in relation to actual or anticipated needs for fat as an energy-yielding substrate for oxidative metabolism[10]. Although the myocardium was found to derive most of its energy requirements from this source, the administration of glucose and insulin could abolish this myocardial extraction of free fatty acids. Estes and colleagues more recently observed that intra-arterial injection of small doses of insulin into one limb rapidly lowered the local arterial concentration of FFA and frequently changed the arterio-venous (AV) difference from negative to positive without affecting the AV difference in the opposite control limb (Estes *et al.*[8]). It was accompanied by a corresponding increase in glucose uptake. The fall in FFA concentration was interpreted to represent a regional suppression of release of FFA. Butterfield and Schless found the arterial concentration of FFA similar in both diabetics and normal controls, but the mean uptake by the forearm was 20 times higher in the controls[5]. Since insulin increased the uptake, it was postulated that one of the metabolic lesions in diabetes was the failure to utilize

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FFA for peripheral metabolism. Earlier studies by Unger *et al.*[18] on myocardial metabolism in diabetics showed a much higher utilization of fatty acids, along with a decreased uptake of glucose, lactate and pyruvate.

Carlson and Pernow reported in 1959 that exercise in healthy subjects lowered the arterial FFA concentration as the exercising leg extracted FFA from the plasma[6]. There was no evidence of hyperglycemia to account for the fall in FFA concentration. Most of the observations were in the nonfasting state, yet no significant difference was observed after a 24-hour fast in a few subjects. It was postulated that the observed extraction of FFA during exercise might be due to metabolism of fatty acids to yield energy via the Krebs cycle, and that FFA was a major form of transport lipid for immediate energy metabolism. Friedberg and associates also found a fall in plasma FFA concentration during exercise which was followed by a significant rise after exertion[9]. They concluded from studies of albumin-bound radiopalmitate that the flux of FFA increased with exercise.

Recently Hamlin *et al.* reported an increase in FFA concentration in normal fasting individuals as a result of neuroadrenergic activity initiated by orthostatic stress of tilting 60° upright[12]. This response could be diminished by the adrenolytic compound, phentolamine, yet it was unimpaired in another patient with bilateral adrenalectomy, and was greatly reduced in a patient with primary autonomic insufficiency. Bogdonoff, Weissler and Merritt found a rise in FFA concentrations during a saline infusion and a fall when a ganglionic blockade was established with Arfonad (trimethaphan camphorsulfonate)[3].

As a preliminary to studies on myocardial metabolism, further studies have been undertaken to compare in cardiac patients the effects of exercise and myocardial stimulation with isoproterenol on peripheral mobilization and apparent utilization of FFA. Isoproterenol was selected because this synthetic catechol amine is more potent than either epinephrine or norepinephrine (Lands and Howard[15]), and has been employed in other hemodynamic studies without any significant increase in total body oxygen consumption (Bruce *et al.*[4]). Carbohydrate utilization and production of excess lactate also were determined in several instances.

Material and Methods. Patients submitted to cardiac catheterization for diagnostic studies have been utilized for this purpose. In most instances the patients were in a fasted state, but exceptions are identified in the protocols. Venous blood was obtained from the iliofemoral system during exercise studies, whereas mixed venous blood was withdrawn from the pulmonary artery in patients who were treated with isoproterenol. Arterial blood was withdrawn from the aorta or brachial artery. Isoproterenol was administered intravenously with 200 μg. in 500 ml. of 5% glucose in water at the rate of 1.5 to 3.0 μg. per minute.

FFA was determined initially by Dole's method[7] and later by Trout's modification in order to eliminate the spurious higher levels due to lactic acid[17]. Glucose, lactate and pyruvate were determined by the methods of Eliot[2] and Turner (modified by Halsey[11]), Barker and Summerson[1], and Segal, Blair and Wyngaarden[16] respectively. Excess lactate (XL) was calculated from changes in lactate and pyruvate concentrations by Huckabee's method[13]. Total metabolism was estimated from the sum of oxygen consumption and anaerobic metabolism as described by Huckabee and Judson[14], using a correction factor of 1.25 to convert XL concentration in whole blood to concentration in blood water. Body water was estimated as 50 to 60% of body weight for these non-edematous patients.

Results. A. EFFECTS OF EXERCISE ON: 1. *FFA Concentrations.* Preliminary observations on 5 patients revealed an average resting arterial FFA concen-

TABLE 1.—EFFECTS OF LEG EXERCISE ON FFA TRANSPORT*

Patients	*Resting*			*Exercise 4 min.*			*Recovery 5 min.*			*Recovery 10 min.*		
	A	*V*	△	*A*	*V*	△	*A*	*V*	△	*A*	*V*	△
	μEq./L.			μEq./L.			μEq./L.			μEq./L.		
Fasting												
Th	1044	1611	–567	854	939	–85	834	1450	–616	846	1368	–522
Ke	995	1579	–584	848	776	72	1094	1276	–182	1060	1431	–371
Mc	1018	1252	–234	948	856	92	1080	1197	–117	1006	1079	– 73
Non-fasting												
Du	577	702	–125	530	511	19	734	880	–146	764	918	–154
Di	1062	1196	–134	1038	976	62	1099	1306	–207	1103	1386	–283
Means												
Fasting	1019	1487	–468	883	857	26	1003	1308	–305	971	1293	–322
Non-fasting	819	949	–130	784	743	41	916	1093	–177	933	1157	–219
Altogether	939	1268	–329	843	811	32	962	1221	–259	955	1236	–281

*Determined by Dole's Method A = arterial concentration V = concentration in iliofemoral veins AV = arteriovenous difference

tration (by the Dole method) of 1019 in 3 fasting individuals, and 819 μM. per L. in 2 non-fasting patients (Table 1). The AV differences were −462 and −130, respectively. With leg exercise for 4 minutes while lying supine, the arterial levels fell to 883 and 784 for the 2 groups of subjects, and returned to approximately the resting performed during the fasting or non-fasting state.

All subsequent observations of FFA were based upon Trout's modification of the Dole method to eliminate falsely high levels due to mobilization of lactic acid. In 7 additional fasting patients, the average resting FFA arterial concentration fell from 811 to 717 ($P<$

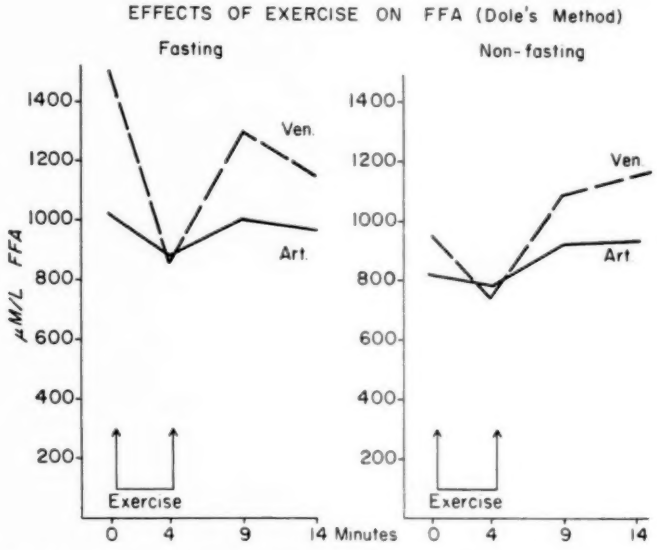

Fig. 1.—Effects of leg exercise on concentration of free fatty acids, as determined by Dole's method, in serum of arterial blood and iliofemoral venous blood. Note the slightly lower levels on the non-fasting subjects.

range, or slightly above, by 5 minutes after exercise. There was no appreciable change in another 5 minutes. The negative AV differences became positive in most instances, with an average of 26 for the fasting, and 41 for the non-fasting patients during exertion. The ratio of the AV difference to the arterial concentration changed from −45 and −16% at rest to 3 and 5% during exertion for the 2 subgroups, respectively. This indicated a change towards increased uptake of FFA with exertion, regardless of the magnitude of the blood flow whether exertion was

.001) with exercise of the legs (Table 2). Concomitantly the average venous concentration in the iliofemoral system fell from 897 to 766 ($P<.001$), while the AV difference changed from an average of −86 at rest to a mean of +24 with exertion ($P<.02$). Again this was interpreted to represent greater uptake of FFA. Since serial samples were not obtained, rates of uptake could not be estimated.

In one instance (G.Co.) the measurements were repeated shortly after IV injection of 52.5 gm. of glucose. Both the arterial and venous FFA concen-

TABLE 2.—EFFECTS OF LEG EXERCISE ON FFA* AND CHO TRANSPORT

	Resting						*Exercise*						
		Arterial		*Gluc.*	*Venous AV△*				*Arterial*	*Gluc.*	*XL*	*Venous AV△*	
Patients	*FFA* μ*M./L.*	*Lact.* *mM./L.*	*Pyr.* *mM./L.*	*mg./* *100 ml.*	*FFA* μ*M./L.*	*FFA* μ*M./L.*	*FFA* μ*M./L.*	*Lact.* *mM./L.*	*Pyr.* *mM./L.*	*mg./* *100 ml.*	*mM./* *min.*	*FFA* μ*M./L.*	*FFA* μ*M./L.*
F. Cov.	1097	—	—	—	1260	−163	936	2.40	.076	82	—	874	62
G. Coo.	548	1.16	.046	95	526	22	464	1.71	.060	94	.040	524	−60
C. Lea.	788	0.67	.031	65	982	−194	716	1.84	.053	59	.138	682	34
J. Tom	906	0.55	.029	70	1174	−268	802	1.02	.045	72	.067	770	32
H. Bay	649	0.50	.034	74	687	− 38	556	1.35	.059	73	.160	509	45
B. Dun	822	0.38	.012	67	792	30	806	0.68	.017	69	.046	832	26
A. Gru.	870	0.54	.024	84	859	11	736	2.34	.033	79	.400	722	14
Means	811	0.63	.029	76	897	− 86	717	1.49†	.049	75	.143	702	22
Stand. Dev.	±18.3	±.25	±.010	±10.8		±112	15.2	±55	±.015	±10.9			±36.1
Mean Diff. ± St. Er.							−93±9	+0.86	+.020			−195±	+108±
								±.56	±.008			10.4	48
Probability							<.001	<.02	<.02			<.001	<.02
G. Co.‡	231	1.78	.042	218	215	16	185	2.15	.035	214	.167	148	37

*Determined by Trout-Estes Method
†Mean for 6 patients with paired values
‡After injecting 52.5 gm. glucose I.V.
(Concentrations are expressed in terms of whole blood)

TABLE 3.—EFFECTS OF ISOPROTERENOL ON FFA AND CHO TRANSPORT

	Resting Supine					*Isoproterenol*					
	Arterial				*Mixed Venous*	*Arterial*					*Mixed Venous*
Patients	*FFA μM./L.*	*Lact. mM./L.*	*Pyr. mM./L.*	*Gluc. mg./100 ml.*	*FFA μM./L.*	*FFA mM./L.*	*Lact. mM./L.*	*Pyr. mM./L.*	*XL mM./L.*	*Gluc. mg./100 ml.*	*FFA μM./L.*
T. Oa.	796	0.82	.029	66	796	1784	0.65	.019	.034	91	1853
A. Pe.	496	0.89	.078	67	540	928	1.29	.071	−.114	76	913
M. Gu.	978	0.44	.037	98	1105	1739	0.52	.025	.049	109	1904
B. Du.	822	0.39	.013	71	792	1320	0.45	.010	.049	82	1282
S. Mo.	1169	0.43	.043	72	1228	1239	0.49	.038	.009	91	1234
F. Bo.	956	0.22	.047	97	920	1348	0.27	.049	.006	85	1356
A. Dr.	724	1.96	.094	89	736	1040	0.95	.033	.046	99	1013
L. Da.	1432	1.02	.043	103	1420	1766	0.87	.091	−.043	131	1816
F. Se.	638	0.68	.038	88	530	905	0.78	.051	−.019	88	837
Means	890	0.76	.047	83	896	1341	0.70	.043	.002	95	1356
Stand. Dev.	±26.6	±0.49	±.023	±13.9	±28.5	±33.3	±0.29	±.024		±16.1	±39.1
Difference						±451	−0.06	−.004		+12	+460
Stand. Error						±15.1	±0.20	±.012		±7.5	±17.1
Probability						<.001					<.001

trations were lowered to less than one-half of the control values (Table 2). Exercise caused, as before, further depression of the FFA as blood sugar rose from 95 to 218 mg. per 100 ml.

2. *Carbohydrate Concentrations.* In the latter 7 fasting patients, arterial glucose concentration averaged 76 mg. per 100 ml. at rest and did not change with exertion. Mean arterial lactate and pyruvate levels increased from 0.63 to 1.49 ($P<.05$) and .029 to .049 ($P<.02$) mM. per L., respectively, while excess lactate (XL) averaged 0.14 mM. per L. with exercise. Injection of glucose in one patient raised glucose and lactate levels, but not pyruvate. Excess lactate with exercise in this subject increased fourfold over the value found prior to producing hyperglycemia.

3. *Body Metabolism.* Oxidative metabolism in these 7 patients increased by an average of 260 ml. of oxygen per minute during this exertion. Anaerobic metabolism, as estimated from production of excess lactate, was equivalent to an average oxygen uptake of 52 ml. per minute. Thus the percentage ratio of oxidative metabolism to total metabolism during exercise ranged from a low of 50% (in a patient with extremely severe calcific aortic stenosis who expired within a month) to 96% (in a patient with a functional systolic murmur) and averaged 78% for the group (normal range is 95 to 99%). Cardiac index increased from a mean of 3.92 to 4.69 L. per M^2. per minute, and AV oxygen difference rose from 39.0 to 61.5 ml. per L. in 3 patients.

B. EFFECTS OF ISOPROTERENOL ON: 1. *FFA Concentrations.* Intravenous infusion of isoproterenol in 9 other patients produced marked increases in mean arterial FFA concentration from 890 to 1341 μm. per L. ($P<.001$) (Table 3). Similar increments occurred in mixed venous blood withdrawn from the pulmonary artery. Thus this synthetic catecholamine readily mobilized FFA.

2. *Carbohydrate Concentrations.* A slight tendency to reduce arterial concentration of lactate from a mean 0.76 to 0.70 was not significant. Similarly there was no substantial change in pyruvate concentration. Although glucose concentration increased in all but 1 patient, the average change was not significant ($P>.10$). Excess lactate production varied from $-.114$ to $+.049$ with an average of $+.002$ mM. per L.

C. COMPARATIVE EFFECTS OF ISOPROTERENOL AND EXERCISE. The mobilization of FFA by isoproterenol is contrasted in Fig. 2 with the utilization associated with exercise. Similarly the mobilization of lactic acid during exercise is contrasted in Fig. 3 with the negligible changes in glucose, lactic and pyruvic acids observed during the administration of isoproterenol.

Discussion. The observed blood levels of FFA are in the previously accepted normal range. The responses to exercise are quite comparable to those reported earlier by Carlson and Pernow[6] and Friedberg *et al.*[9]. The changes in arterial concentration of lactate, pyruvate and excess lactate with exercise are similar to those found by Huckabee and Judson in previous studies of cardiac patients[14].

The advantage of calculating excess lactate produced during exercise is the opportunity to determine what fraction of the total metabolism is accomplished anaerobically by oxidation processes. Since the latter are often limited, and to different degrees in patients with inadequate peripheral perfusion due to heart disease, this measures the magnitude of anaerobic metabolism responsible for the oxygen debt.

Although the total metabolic response to exercise could be estimated

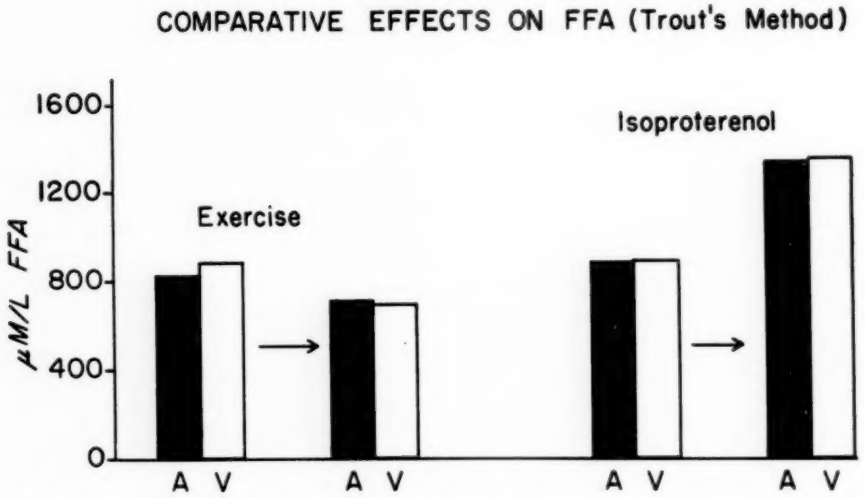

Fig. 2.—Comparative effects of leg exercise and IV infusion of isoproterenol on concentrations of free fatty acids in arterial and venous blood. Note the reversal of peripheral AV difference with exercise, and lack of difference in arterial and mixed venous concentrations with isoproterenol.

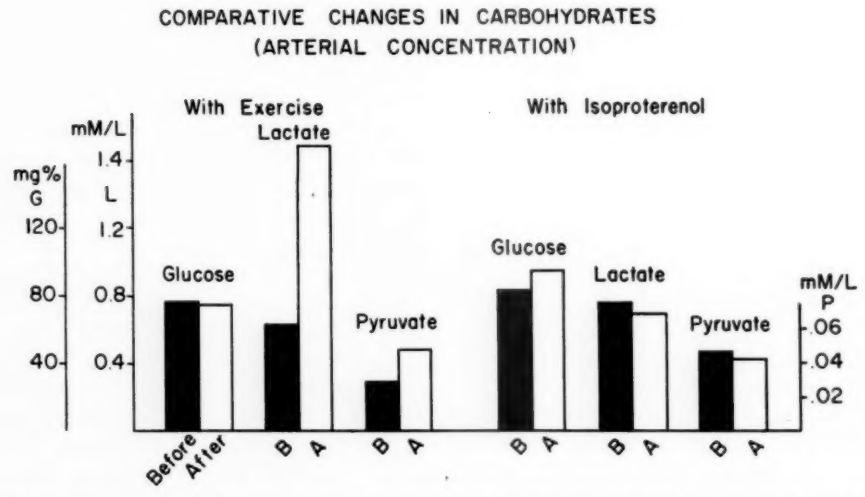

Fig. 3.—Comparative changes in carbohydrate substrates in arterial blood as a result of increasing myocardial work by means of exercise and by means of pharmacologic stimulation with isoproterenol. Note the significant increase in lactate with exercise.

in these studies, the available data are not sufficient to permit calculation of the proportion of oxidative metabolism supported by FFA and carbohydrates. Since there was no decrease in glucose, lactate or pyruvate concentrations, while FFA diminished, it is quite likely that a major contribution was made by lipids rather than carbohydrates. Indeed, the arterial concentration of lactate and pyruvate increased. It is difficult, however, to define this further when the venous blood sampled represents contributions of blood derived from exercising skeletal muscles, concomitant mobilization from adipose depots, as well as from inactive tissues. Furthermore, there may be fluctuations in the hematocrit related to chloride shifts that affect the blood levels as noted by Carlson and Pernow[6].

Isoproterenol appeared to be more effective in mobilizing FFA from the adipose tissues than in mobilizing blood sugar. In this regard, it is as potent as epinephrine. This greater mobilization of FFA was not accompanied by any obvious change in uptake. Although total body oxygen consumption increased but slightly, myocardial oxygen consumption undoubtedly increased considerably along with the increased cardiac output. Therefore, pertinent changes in metabolic utilization of lipids and carbohydrates probably would be limited to the myocardium under these circumstances.

Summary. 1. Arterial and venous concentrations of free fatty acids (FFA) were studied before and during leg exercise or during intravenous isoproterenol in 20 cardiac patients: arterial concentrations of glucose, lactate and pyruvate were also measured in 15 instances.

2. Leg exercise increased aerobic and anaerobic metabolism and lowered the arterial and iliofemoral venous FFA concentrations significantly. Increased uptake was inferred by a change in arteriovenous differences. Parenteral glucose lowered FFA levels and raised excess lactate production with exertion in one patient.

3. Isoproterenol markedly increased FFA levels and cardiac output without significantly altering whole body metabolism.

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(Interlingua on page 43)

THROMBOCYTOSIS: A POSTSPLENECTOMY COMPLICATION IN AGNOGENIC MYELOID METAPLASIA

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Among the myeloproliferative disorders, thrombocythemia, a state of persistent elevation of circulating platelets, is well recognized (Gunz[15]). It can be primary (idiopathic, essential) or secondary, occurring in association with a variety of disorders such as leukemia, polycythemia, carcinoma, splenic atrophy or following splenectomy. The manifestations of bleeding or thrombosis, or both, seen with this disorder are also well recognized even though the pathological physiology has not yet been completely explained. A review of the literature shows that treatment with triethylene melamine (Nelson and Stevenson[31]), Busulfan (Marchal *et al.*[29]) and radioactive phosphorus (Alajouanine *et al.*[1], Baikie, Cunningham and McAlpine[3], Cartwright *et al.*[7], Coliez, Tubiana and Alagille[8], Fountain[13], Gunz[15], Laporte *et al.*[23], Tubiana and Boiron[38], Woodrow and Cope[39]) has met with variable success in the control of the hemorrhagic phenomena. Although reports of the course following splenectomy in patients with myeloid metaplasia are available (Brewster and Wallenman[5], Bukh and With[6], Dustin[10], Duvoir and Pallet[11], Edwards[12], Heller, Lewisohn and Palin[17], Levinson and Limarzi[26], Polowe[33], Skinner and Sophian[35]), the hemorrhagic and thrombotic manifestations that in our experience regularly follow splenectomy for this disorder have not been emphasized. This report details the courses of 6 patients with agnogenic myeloid metaplasia who were splenectomized and subsequently required treatment for control of symptomatic thrombocytosis.

Methods. Standard hematologic techniques were employed for determination of the red and white blood cell counts. Hemoglobin values were determined photoelectrically. Cover-slip films of the peripheral blood and marrow were stained with Wright's stain. Brilliant cresyl blue preparations were counterstained with Wright's stain. Platelet counts were done by phase microscopy or enumerated on the brilliant cresyl blue preparation, or both. Normal values were from 200,000 to 400,000 per c.mm. Thrombocytosis was expressed as follows: 1+ representing 400,000 to 600,000 platelets per c.mm.; 2+ representing 600,000 to 800,000 platelets per c.mm.; 3+ representing 800,000 to 1,000,000 platelets per c. mm.; 4+ representing more than 1,000,000 platelets per c.mm. The radioactive phosphorus in each instance was administered intravenously.

Case Reports. Case 1. D.B. (UH #832009) (Fig. 1). This 42-year-old white woman was first seen at Simpson Memorial Institute in January, 1956. In 1945, in the course of prenatal examination, splenomegaly had been noted. Although asymptomatic, hematological studies at that time led to the diagnosis of myeloid metaplasia. In July, 1946, during the fourth month of pregnancy, splenectomy was performed without incident. The pathological examination confirmed the diagnosis of myeloid metaplasia. She subsequently was delivered of a normal full-term infant. Fol-

lowing splenectomy, hemorrhagic manifestations developed and became increasingly troublesome in the form of development of large hematomas, ecchymosis on slight provocation, repeated epistaxis, and constant gingival bleeding. Because of the latter difficulty, increasing with peridontal disease, hematological consultation was requested by her peridontist. Through the years she had noted progressive hepatomegaly. A single 3-month course of prednisone in 1955 had not affected the bleeding phenomena.

Wintrobe sedimentation rate, corrected, 1 mm. per hour. Her white blood cell count corrected was 44.570 per c.mm. with the following differential: blasts 4%, myelocytes 1%, metamyelocytes 1%, bands 27%, segmented polymorphonuclears 43%, large lymphocytes 8%, small lymphocytes 3%, monocytes 3%, eosinophils 8%, basophils 2%. There was marked polychromasia, hypochromia, anisocytosis, and poikilocytosis. Target cells were numerous. There were 29 nucleated red blood cells per 100 white blood cells. The reticulo-

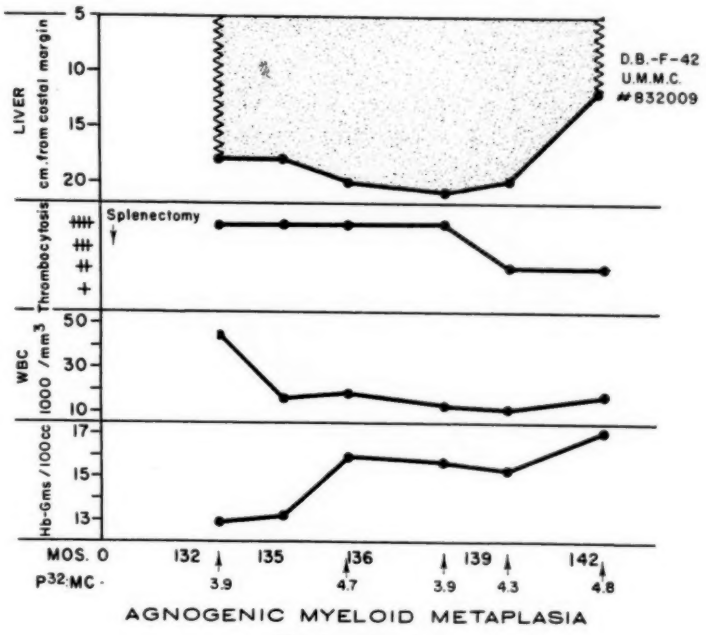

Fig. 1.—Case 1.

On physical examination, she appeared chronically ill. Scattered bruises were present on the lower extremities. There were no petechiae. The oral mucosa was covered with fresh blood, constantly oozing from gingival margins. The abdomen was protuberant but soft, and a firm non-tender liver was palpable 18 cm. below the right costal margin on deep inspiration. The left lobe extended into the left upper quadrant.

Laboratory studies showed the hemoglobin to be 12.9 gm.%, the hematocrit 53 vol.%, the red blood cell count 6,600,000 per c.mm., with the mean corpuscular volume (M.C.V.) 80 c. micra, and the mean corpuscular hemoglobin concentration (M.C.H.C.) 24.4%. The cytes were estimated at 3%. On the film the platelets were markedly increased with large and atypical forms present. Platelet count by phase microscopy was 2,000,000 per c. mm. Sternal marrow aspirate was hypocellular but showed large sheets of platelets. Complete coagulation studies (Table 2) were within normal limits except for a prolonged bleeding time (Duke, 17 min.). Liver function studies were normal except for an alkaline phosphatase of 44.5 King-Armstrong units. Long bone roentgenologic survey as well as films of the skull and spine were entirely within normal limits.

Because of the excessive thrombocytosis with associated hemorrhagic phenomena, the

TABLE 1.—A SUMMARY OF THE RECORDED RESULTS OF SPLENECTOMY IN AGNOGENIC MYELOID METAPLASIA

No.	*Author*	*Year*	*Age*	*Sex*	*Preoperative Diagnosis*		*Results after Splenectomy*
1–54	Bukh and With	1945	18 to 64	25 M 27 F 2 not stated	1. Banti's disease:	15	
					2. Idiopathic thrombocytopenic purpura:	4	40% died within one month
	collected from the literature, 1902 to 1944; includes Jackson 3 cases, Duvoir 1 case				3. Mechanical inconvenience:	8	60% died within one year
					4. Hemolytic jaundice:	4	
					5. Splenic anemia:	2	20 to 30% followed by amelioration of more than one year's duration.
					6. Tuberculosis spleen:	1	
					7. Uncertain diagnosis:	2	
					8. Not specified:	18	
55	Reich and Rumsey	1942	52	M	Banti's disease		Lived 5 years; 20 hospitalizations; 50 blood transfusions; no change.
56			44	F	Neoplasm of spleen		Five hospitalizations; no change.
57			48	F	No diagnosis		Hodgkin's disease; condition worse.
58			55	F	Banti's disease		No betterment; condition worse.
59	Brewster and Wollenman	1942	25	F	Severe hemolytic anemia		Died 13 days postoperatively.
60	Polowe	1944	29	F	Idiopathic thrombocytopenic purpura; 8 months pregnant		No mention.
61	Dustin	1947	51	F	Banti's disease		Severe anemia; died 6 years later; death unexplained.
62	Levinson and Limazi	1947	49	F	Agnogenic myeloid metaplasia		Died 6 weeks after splenectomy; cardiorespiratory pathology.
63	Heller, Lewisohn Palin	1947	58	F	Not stated		Two years after splenectomy was in poor health; epistaxis; no betterment.
64	Skinner and Sophian	1951	38	M	Gastrointestinal bleeding		Five years later no evidence of agnogenic myeloid metaplasia.
65	Edwards	1951	56	M	Not stated		When reported, well 4 months after splenectomy; lost to follow-up.
66			46	M	Agnogenic myeloid metaplasia (severe hemolysis)		When reported 2 years after splenectomy, active at his trade: one blood transfusion every 5 to 6 weeks, increase in WBC.

67	Green	1953	46	M	Banti's disease	Survived 4¾ years; died after gastrectomy for peptic ulcer; some betterment.
68			41	M	Not stated	Surviving 4½ years at time of report; increase in WBC and RBC.
69			64	M	Enlarged spleen	Survived 20 years; died cerebrovascular accident.
70			61	M	Banti's syndrome	7½ years after splenectomy in good health.
71			52	M	Thrombocytopenia and hemolytic anemia	Increase in platelets; hemolytic anemia corrected.
72	Loeb	1953	54	F	Agnogenic myeloid metaplasia with hemolytic anemia	No transfusion for 19 months when reported; active at her trade.
73			67	F	Agnogenic myeloid metaplasia with hemolytic anemia	Died 8 days after splenectomy; platelets 3,500,000 per c. mm.; cerebrovascular accident.
74	Korst	1956	57	M	Agnogenic myeloid metaplasia with hemolytic anemia	Less blood transfusions needed; died one year later: acute myelomonocytic leukemia.
75	Meilleur and Meyers	1960	42	F	Agnogenic myeloid metaplasia; fourth month of gestation	Alive 15 years later; thrombocythemia with severe bleeding; erythrocytosis increased.
76			58	M	Agnogenic myeloid metaplasia; severe hemolysis	Alive 3 years later; thrombocythemia with thrombosis; improved.
77			49	M	Congestive splenomegaly (Banti's syndrome)	Alive 4 years later; thrombocythemia with thrombosis; active at his trade.
78			41	F	Incidental splenectomy	Alive 6 years later; thrombocythemia asymptomatic.
79			68	M	Chronic granulocytic leukemia	Expired 3½ years later; no benefit.
80			64	F	Congestive splenomegaly	Expired 5 years later: cerebrovascular accident.

patient was given 3.9 mc. of radioactive phosphorus intravenously. Two months later, she reported that for 6 weeks subsequent to the administration of the radioactive phosphorus, she had noted no change in her hemorrhagic status. However, 2 weeks before her return, the bleeding stopped and had not recurred. Hematological examination at that time revealed a reduction in the white blood cell count to 15,000 per c.mm. without change in the differential. The hemoglobin remained at 13.2 gm%. There had been a significant reduction of platelets although they were still increased in number. Peridontal treatment was initiated without excessive bleeding.

COMMENT: The early age (32 years old) of onset of myeloid metaplasia is of particular interest. She is the youngest patient seen at Simpson Memorial Institute with this disorder. Noteworthy also was her pregnancy (G iii, P o) and that she underwent splenectomy uneventfully during the fourth month of gestation. Her hemorrhagic diathesis presented the characteristics of a coagulation defect. Steroids did not modify the bleeding. Relief of her hemorrhagic manifestations was achieved by control of the thrombocythemia. She had progressive hepatomegaly. With the correction of her thrombocytosis, erythrocytosis increased.

TABLE 2.

DATE PATIENT	January, 1956 D.B.	August, 1957 J.H.
Clinical Status When Tested	Bleeding	Not Bleeding
TESTS		
Platelets per c. mm.	2,000,000	515,000
Bleeding time (Duke)	17 min.	4 min.
Clot retraction	good, 1 hour	good, 1 hour
Clotting time (Lee and White) Silicone	10 min., 30 sec. 32 min.	5 min., 30 sec. — — —
First-stage Prothrombin time (Quick)	13 sec.	12.5 sec.
Factor V estimation	17.6 sec.	25.2 sec.
Factor VII estimation	37 sec.	22.8 sec.
Thromboplastin Generation Test	18 sec.	17 sec.
Anticoagulants in platelets in plasma	— — — — — —	Absent Absent
Fibrinogen	350 mg.	— — —

Between June, 1956, and February, 1957, she received a total of 17.79 mc. of radioactive phosphorus in 4 doses. The platelets remained slightly increased. However, bleeding did not recur. Her erythroid values increased progressively and in February, 1957, it was apparent that erythrocytosis was also part of her hematological problem. Her hemoglobin was 17 gm.%, hematocrit 63 vol.%. Ten milligrams of triethylene melamine were given orally. In 1957, the patient moved to a distant place and has not been seen by us since. However, follow-up information reveals that her platelets increased to 4,000,000 per c.mm. and that she had severe bouts of gastrointestinal bleeding. The administration of radioactive phosphorus again was effective in controlling the hemorrhagic phenomenon.

CASE 2. W.L. (UH #708297) (Fig. 2). This 58-year-old-white man was first admitted to the Simpson Memorial Institute in July, 1951. For the preceding 9 years he had episodes of postprandial "bloating" which had been progressive in severity. For 2 years prior to admission, he had had attacks of alternating diarrhea and constipation. During the year prior to admission he had noted increasing ease of fatigue, tiredness, and weakness. There had been a 20-lb. weight

loss. Pallor had been present for 8 months and he was first told that he was anemic about 5 months prior to admission.

On physical examination he appeared debilitated and chronically ill. The spleen was palpable at rest 10 cm. below the left costal margin in the midclavicular line. The liver was felt 4 cm. below the right costal margin on deep inspiration.

many proerythroblasts and early normoblasts were seen.

The patient was given oral cortisone, 300 mg. daily for 9 days and then 75 mg. daily with some increase in the erythroid values. However, his spleen increased in size. In November, 1951, he received a total of 625 roentgens over the splenic region without improvement. During the subsequent 4 years

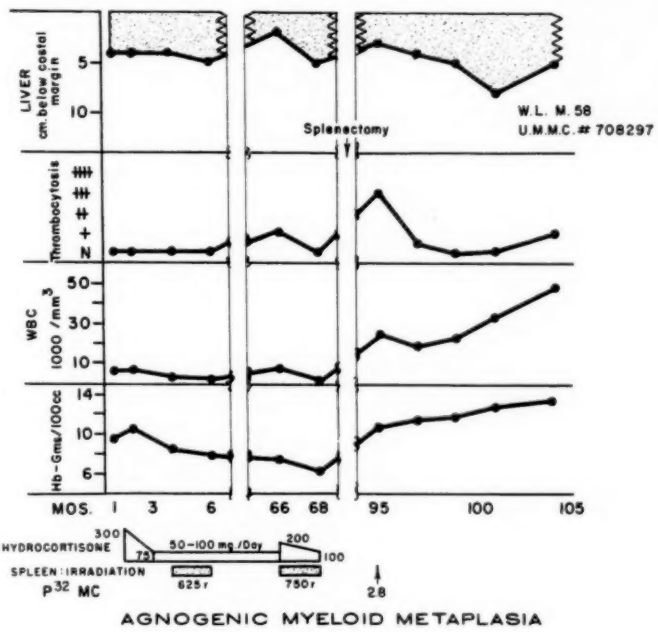

Fig. 2.—Case 2.

The red blood cell count was 3,900,000 per c.mm., white blood cell count 7,050 per c.mm. Hemoglobin was 9.8 gm.%, hematocrit 33 vol.%, M.C.V. 85 c.micra, and M.C.H.C. 29.6%. The Wintrobe sedimentation rate, corrected, was 14 mm. per hour. The white blood cell count differential was normal, but there was marked anisocytosis, poikilocytosis, polychromasia, and some basophilic stippling of red blood cells. Platelets were present in normal numbers. Liver function studies were normal. Upper gastrointestinal roentgenograms showed transient pylorospasm, but no evidence of intrinsic abnormality. Sternal marrow aspirate was very hypocellular with a moderate amount of fat and rare myeloid elements. Splenic aspiration yielded a cellular sample with active myelopoiesis. Megakaryocytes were numerous, and

he continued to receive cortisone, 50 to 100 mg. daily and was moderately well. In 1956 he was hospitalized elsewhere because of jaundice which subsequently cleared on bed rest. Prednisone, 20 mg. daily, was substituted for cortisone. In October, 1956, he began to feel weak and tired, he was pale and had shortness of breath and a feeling of heaviness in his legs. His spleen was 20 cm. below the left costal margin at rest, while the liver descended 4 cm. below the right costal margin on deep inspiration. The hemoglobin was 7.6 gm.%. He was readmitted and the presence of hemolysis was established. Hydrocortisone, 200 mg. daily, was begun. After 14 days it was tapered to 100 mg., then to 80 mg. daily. His spleen receded to 15 cm. below the left costal margin at rest. In December, 1956, he received 375 roentgens to

each of 2 splenic fields with no change in his status.

Between January, 1957, and May, 1959, he was treated elsewhere. In April, 1957, splenectomy was performed without difficulty. However, 10 months later he noted the onset of intermittent episodes of pain, swelling and redness in both lower extremities, associated with chills and fever. Despite treatment with bishydroxycoumarin, bed rest and elevation of his extremities, recurrent thrombosis occurred. He received prednisone, 5 mg. daily and Busulfan, 2 mg. twice weekly for one year without improvement. He returned to the Simpson Memorial Institute in May, 1959, with thrombosis in the forearm and of both greater saphenous veins in the mid-thigh region. The liver was palpable 3 cm. below the right costal margin on deep inspiration. His hemoglobin was 10.7 gm.%, hematocrit 37 vol.%, red blood cell count 3,800,000 per c.mm., and leukocyte count 25,000 per c.mm. His platelets ranged from 800,000 to 1,000,000 per c.mm. There was no evidence of hemolysis. The patient appeared well but was in moderate discomfort. Prednisone and bishydroxycoumarin were discontinued and radioactive phosphorus, 2.8 mc., was given intravenously. In July, 1959, the platelet count was normal but large and bizarre forms were present. His hemoglobin was 11.2 gm.%, hematocrit 37 vol.%. He has had no recurrence of thrombotic episodes to date. When last seen in May, 1960, the platelet count remained normal.

COMMENT: The course of this patient's myeloid metaplasia did not seem to be altered by steroids or Roentgen-ray therapy. Splenectomy was necessary to control hemolysis. His liver, although enlarged from the start further increased in size after splenectomy. With the post-splenectomy increase in platelets, thrombotic complications occurred. The benefit achieved from a single dose of radioactive phosphorus was impressive.

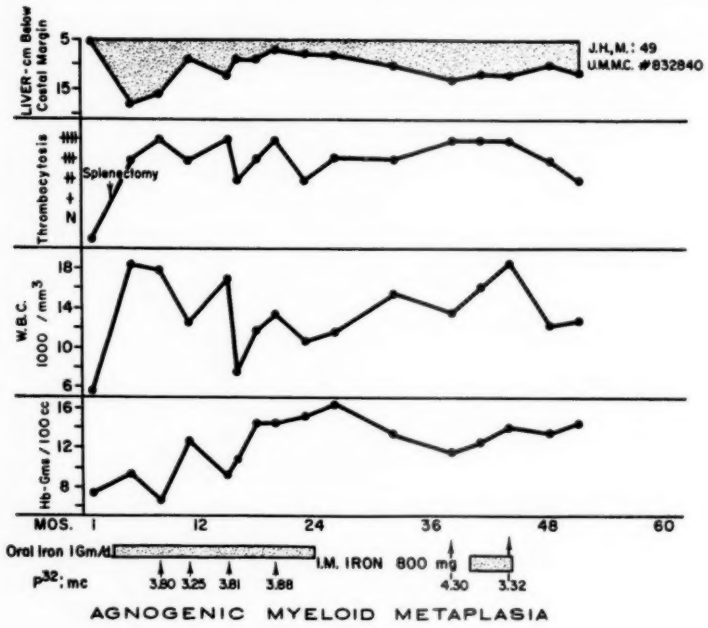

Fig. 3.—Case 3.

CASE 3. J.H. (UH #832840) (Fig. 3). This 49-year-old white man was referred to the Surgical Service of the University of Michigan Medical Center in January, 1956, with a diagnosis of bleeding esophageal varices. His spleen was palpable 11 cm. below the left

costal margin at rest, and the liver 8 cm. below the right costal margin on deep inspiration. A splenoportogram showed extrahepatic portal vein block with cavernous transformation of the portal vein. In addition, marked esophageal and gastric varices were visualized. A splenectomy and spleno-renal shunt were done. Histologic examination of the spleen revealed extramedullary hematopoiesis. Subsequently hematologic evaluation established the diagnosis of myeloid metaplasia.

Postoperatively, his hemoglobin was 8.2 gm.%, hematocrit 25 vol.%, red blood cell count 2,700,000 per c.mm., M.C.V. 93 c. micra, M.C.H.C. 29.6%, and the Wintrobe sedimentation rate, corrected, 5 mm. per hour. White blood cell count was 5,500 per c.mm. with polymorphonuclear bands 4%, polymorphonuclear segments 74%, large lymphocytes 9%, small lymphocytes 4%, monocytes 5%, eosinophils 2%, basophils 2%. The red cells showed marked anisocytosis, marked poikilocytosis and mild polychromasia. There was one nucleated red blood cell per 100 white blood cells. The reticulocytes were estimated at 3%. Platelets were moderately decreased in number with bizarre forms present. One megakaryocytic fragment was seen. A sternal marrow aspirate was hypocellular with sheets of platelets present.

In June, 1956, he had a further episode of hematemesis and a thrombophlebitis of the right leg. Microcytic hypochromic anemia and marked thrombocytosis were present. Iron therapy was continued and radioactive phosphorus, 3.8 mc., was given. In November, 1956, 3.25 mc. of radioactive phosphorus was given because of persistent thrombocytosis. In December, 1956, he was hospitalized for 19 days because of hematemesis. In March, 1957, 3.81 mc. of radioactive phosphorus was administered and in August 3.88 mc. Thereafter his hematocrit and hemoglobin rose to normal limits and there was modest reduction in the thrombocytosis. He remained asymptomatic until September, 1958, when again he had hematemesis and melena. Intramuscular iron to a total dose of 800 mg. was given. His platelets continued to be moderately increased and in February, 1959, and August, 1959, he received additional radioactive phosphorus. His liver was 12 cm. below the right costal margin on deep inspiration. However, he has been free of bleeding since September, 1958. When last seen in June, 1960, his hemoglobin was 13.9 gm.% and the thrombocytosis minimal. He was feeling entirely well, and was active, working at his trade without difficulty.

COMMENT. In this instance agnogenic myeloid metaplasia was confused preoperatively with ordinary congestive splenomegaly. The demonstration of esophageal varices added to the confusion, which might, however, have been resolved by more extensive hematologic studies preoperatively. It is of interest that the hematemeses were not effectively controlled after establishment of the spleno-renal shunt until the thrombocytosis that followed splenectomy was modified.

CASE 4. V.K. (UH #796097) (Fig. 4). This 41-year-old woman was first seen at Simpson Memorial Institute in October, 1954. She had been well until about one year previously when she developed progressive weakness and tiredness. In June, 1954, she noted a rather severe sharp cramping type of pain extending over the entire upper abdomen. This persisted for 2 weeks, at which time she was hospitalized. After 2 weeks of intensive study, a celiotomy was performed. Because of uncontrollable bleeding from the splenic biopsy site, the spleen was removed. Histologic sections of the spleen were reported as showing evidence of extramedullary hematopoiesis with numerous megakaryocytes present. She recovered from the operation without incident. Subsequently her abdominal pain was relieved. However, weakness and fatigue persisted, and she was referred here for further evaluation.

On physical examination she was a well-developed woman, somewhat anxious and depressed. The liver was slightly tender and palpable 8 cm. below the right costal margin in the midclavicular line on deep inspiration. The remainder of the physical examination was not remarkable.

On admission her hemoglobin was 11.7 gm.%, hematocrit 39 vol.%; red blood cell count was 4,500,000 per c.mm., white blood cell count 15,000 per c.mm. The platelets were in excess of 1,000,000 per c.mm. Sternal marrow aspirate was diffusely hypocellular with decreased erythropoiesis and granulopoiesis. Large sheets of platelets were present on the films. All other laboratory data were within normal limits except for a bromsulphalein retention of 15.3% at 45 minutes. Because of the thrombocytosis, 3.05 mc. of radioactive phosphorus was administered. Between December, 1954, and November, 1959, the platelet count varied between 400,000

and 800,000 per c.mm. and she received a total of 13.8 mc. of radioactive phosphorus in 3 doses. She has remained fatigued throughout this period of observation. There has been no episode of hemorrhage or thrombosis. In November, 1959, her thrombocytosis was minimal and when last seen in March, 1960, her status was unchanged.

nomena. Long-standing diabetes was in good control. In 1951 splenomegaly had been noted. The white blood cell count was said to have been elevated and the erythroid values normal. A diagnosis of chronic granulocytic leukemia had been made. He was treated with Fowler's solution and irradiation to the spleen without benefit. Splenectomy was per-

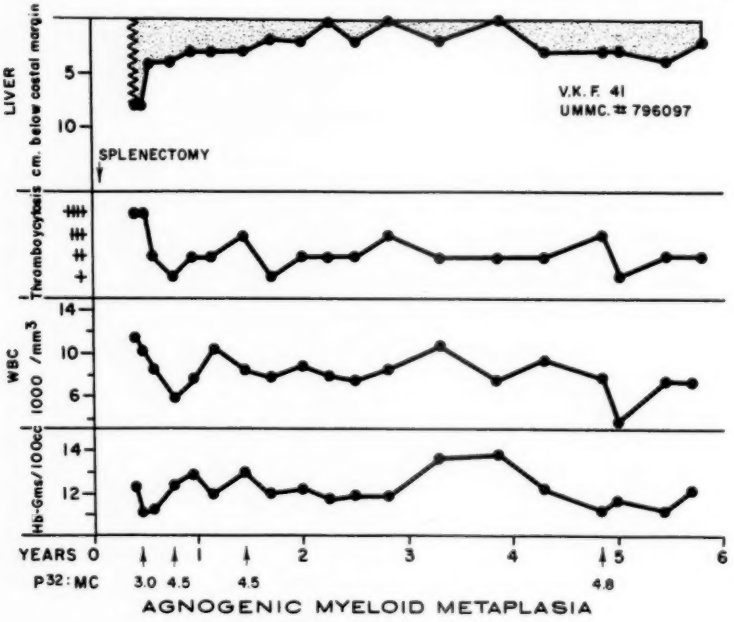

Fig. 4.—Case 4.

COMMENT. This patient did not present thrombotic or hemorrhagic manifestations after splenectomy despite a substantial and sustained increase in platelets. We would like to believe that this relates to the fact that radioactive phosphorus was initiated soon after her operation before any hemorrhagic or thrombotic episodes occurred. Administration of radioactive phosphorus was repeated as indicated by platelet counts rather than awaiting clinical symptoms.

CASE 5. A.F. (UH #796562) (Fig. 5). This 68-year-old white man was first seen at the Simpson Memorial Institute in October, 1954, because of recurrent hemorrhagic phe-

formed in March, 1953, following which he was told he did not have leukemia. In July, 1953, he first noted increase in bruising and epistaxis which were progressive.

Physical examination revealed a weak, chronically ill man with moderate bleeding from the nose. The heart was slightly enlarged to the left of the midclavicular line. A rough, blowing systolic murmur was best heard at the aortic valve and along the left sternal border. The liver was palpable 8 cm. below the right costal margin in the midclavicular line on deep inspiration. The left lobe was palpable 14 cm. below the xiphoid. There was 2+ pitting edema of the feet and ankles.

The hemoglobin was 6.7 gm.%, hematocrit 23 vol.%, red blood cell count 2,700,000 per c.mm., white blood cell count 45,800 per c.mm. with progranulocytes 1%, polymorpho-

nuclear bands 10%, polymorphonuclear segments 75%, large lymphocytes 3%, monocytes 3%, basophils 2%, eosinophils 7%. There was marked anisocytosis and poikilocytosis and severe hypochromia. The platelet count was greater than 1,000,000 per c.mm. Sternal marrow aspirate was hypocellular but with large clumps and sheets of platelets. His nonprotein nitrogen was 58 mg. per 100 ml., bromsulphalein retention 6.3% at 45 minutes, was 27,200 per c.mm. with no change in his differential. Radioactive iron studies and serum iron studies were consistent with the impression that the anemia was due to severe iron deficiency. Gastrointestinal roentgenograms were negative. Radioactive phosphorus, 3.9 mc., was again administered and the patient placed on iron medication.

Severe epistaxis in early February, 1955, required 2 units of blood. In March, 1955,

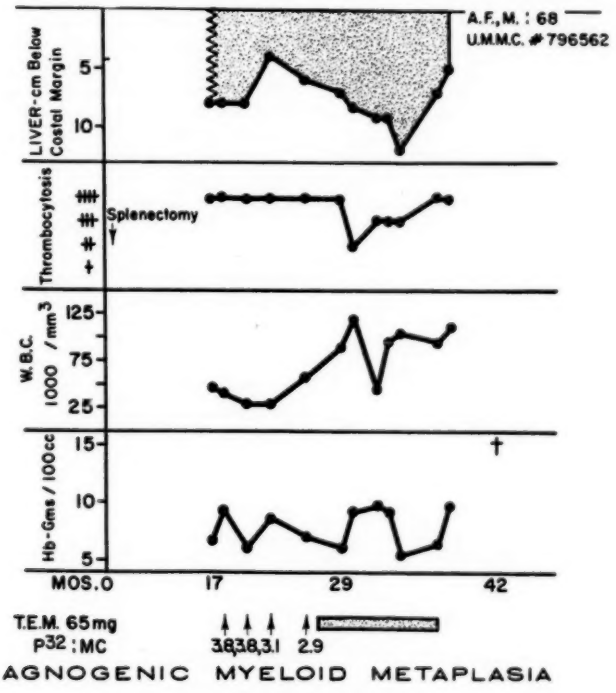

Fig. 5.—Case 5.

prothrombin consumption 67% with prothrombin time (Quick) 12.2 seconds. All other tests were within normal limits.

Because of the marked thrombocytosis to which the hemorrhagic diathesis was ascribed, 3.6 mc. of radioactive phosphorus were administered. Blood transfusions were necessary to maintain the hemoglobin between 10 and 11 gm.%. On discharge he was slightly improved. Subsequently he was readmitted in January, 1955. He had not noted further bleeding or bruisability and had not received blood transfusion. His hemoglobin was 6 gm.%, hematocrit 25 vol.%, red blood cell count 3,600,000 per c.mm., M.C.H.C. 24%, M.C.V. 69.5 c. micra. The white blood cell count radioactive phosphorus, 3.1 mc., was given because of persistent thrombocytosis. Another dose of 2.9 mc. was injected in June, 1955. Despite absence of bleeding, he required numerous transfusions during the summer and in September, 1955, he was readmitted. It was thought that a hemolytic component was present. He was started on hydrocortisone orally, 200 mg. daily; triethylene melamine to a total dose of 12.5 mg. was given in an attempt to decrease his thrombocytosis. After 8 days, the hydrocortisone was tapered and after receiving 5 units of whole blood, he was discharged improved.

In December, 1955, he required multiple blood transfusions. Two courses of triethylene

melamine to a total of 20 mg. were given. Because of severe prolapsed hemorrhoids, a hemorrhoidectomy was performed. In January, 1956, because of intractable urinary retention, a suprapubic cystostomy was done which subsequently was complicated by poor wound healing and persistent oozing and urinary drainage around the site of the tube. His subsequent course was one of progressive deterioration. In October, 1956, he expired at home with heart failure, urinary tract infection and uncontrolled diabetes mellitus.

CASE 6. J.S. (UH #804663) (Fig. 6). This 64-year-old white woman was first seen by us in February, 1955. Her blood pressure had been moderately elevated for the previous 17 years. Intermittent left upper quadrant discomfort had been present for 10 years. In 1943, a flat plate of the abdomen had shown an enlarged spleen. Blood studies were not done at that time. In 1953, during exacerbation of her abdominal discomfort, splenomegaly and an anemia were noted. (Hemoglobin 9.6 gm.%, red blood cell count

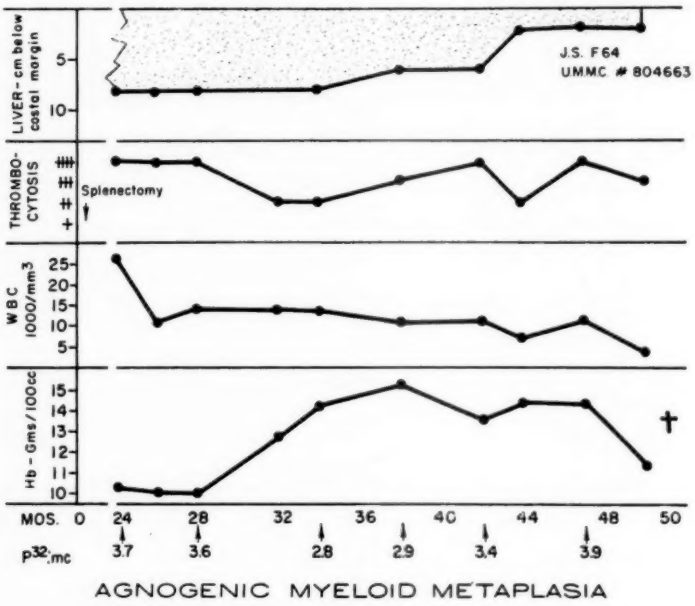

Fig. 6.—Case 6.

COMMENT. Agnogenic myeloid metaplasia has been confused frequently with chronic granulocytic leukemia. The differential diagnosis usually is not difficult if sufficient attention is directed to red cell morphology and marrow composition. In either disorder the indications for splenectomy are limited and did not exist in this patient. The symptomatic thrombocytosis that followed splenectomy was unresponsive to treatment with radioactive phosphorus and triethylene melamine.

3,100,000 per c.mm., white blood cell count 6,100 per c.mm.). Splenectomy was performed. The histological diagnosis was reported as agnogenic myeloid metaplasia. In 1954, following a fall, she sustained a fracture of the transverse process of the second lumbar vertebra. Despite numerous medications, her anemia was not corrected. Progressive tiredness, weakness, ease of bruisability and moderate epistaxis were noted. She was referred here for further treatment.

On physical examination, her blood pressure was 210/100 right arm reclining. There was a grade II, soft blowing systolic murmur heard over the entire precordium. Her liver was palpable 8 cm. below the right costal

margin on deep inspiration. There was 2+ pitting edema of the feet, ankles and mid-leg regions.

Her laboratory data were as follows: hemoglobin 10.4 gm.%, hematocrit 34 vol.%, red blood cell count 3,400,000 per c.mm., white blood cell count 25,250 per c.mm. The white blood cell count differential was not remarkable. The erythrocytes showed marked anisocytosis, poikilocytosis and leptocytosis, moderate spherocytosis and polychromasia. There were 2 nucleated red blood cells per 100 white blood cells. The platelets were in excess of 1,000,000 per c.mm. Large and bizarre forms were present. Tests of liver function were within normal limits. Non-protein nitrogen was 43 mg. per 100 ml., creatinine clearance was 98 liters per 24 hours. Sternal marrow aspirate was hypocellular with large sheets of platelets.

Because of the marked thrombocytosis, 3.7 mc. of radioactive phosphorus were given with only modest effect on the thrombocytosis. However, the epistaxis ceased and she had less ease of bruisability. During the next 24 months, she received a total of 17.6 mc. of radioactive phosphorus and remained asymptomatic until January, 1957, when moderate repeated epistaxis recurred. Attempts to lower her blood pressure were unsuccessful. In May, 1957, while at home, she had an abrupt hemiplegia. The systolic blood pressure was 280 mm. Hg. She expired within 3 hours.

COMMENT. Presumably this patient sustained a cerebrovascular accident. In the face of a long history of hypertension, it is difficult to state the role her thrombocytosis may have played.

Discussion. Until recent years, the patient with agnogenic myeloid metaplasia was thought to be dependent on his enlarged spleen for hemopoiesis. Thus irradiation to the spleen or splenectomy were considered contraindicated. This view was supported by observations such as those of Jackson, Parker and Lemon[19] who, in 1940, reported 10 patients of whom 3 had had irradiation to the spleen and 3 had had splenectomy. Of the 3 who had had irradiation, all died within 2 years, 2 of them within 2 weeks. Of the 3 that had had splenectomy, 2 expired within 6 weeks and the other within one year. The remaining 4, treated only symptomatically, were observed for 22 months to 16 years. Reich and Rumsey[34] in 1942 also gave warning of the danger incurred by splenectomy and irradiation to the spleen. Bukh and With[6] in 1945 collected from the literature 54 cases of agnogenic myeloid metaplasia in whom splenectomy had been performed. Forty per cent had died within one month and 60% within one year. Approximately 25% had amelioration of their transfusion requirements for at least a year (Table 1).

In 1947 Dustin[10] reported a 6-year-follow-up after splenectomy. His patient was clinically better. In 1951 Skinner and Sophian[35] reported a similar case. Edwards[12], also in 1951, recalls 2 cases of agnogenic myeloid metaplasia, splenectomized in 1942 and 1949, respectively at the height of the debate on the compensatory theory. Both did well after splenectomy. Duvoir and Pallet[11] in 1941 reported a similar experience. Loeb, Moore and Dubach[28], Green *et al.*[14], Korst, Clatanoff and Schilling[22], Cartwright *et al.*[7] hold the view that splenectomy may be indicated in myeloid metaplasia if there is associated hemolysis.

In agnogenic myeloid metaplasia, splenic enlargement is an integral manifestation of the fundamental proliferative process, and as pointed out by Hutt, Pinniger and Wetherby-Mein[18] is not a compensatory mechanism for reduced marrow hemopoiesis. In 1957, Linman and Bethell[27] reviewed the natural course of agnogenic myeloid metaplasia and discussed the embryological potentialities of mesenchymal tissues and their relationship to the enlarged spleen and liver in this disorder.

Indications for splenectomy in agnogenic myeloid metaplasia are limited. They include rupture of the spleen or the supervention of hypersplenism in

the form of hemolytic anemia or thrombocytopenic purpura not controllable by medical measures such as steroids or by irradiation. The operative risk is high. This is contributed to by the debilitated status of most patients by the time indications for splenectomy become apparent, and to us this consideration has been an important deterrent to operation in some patients in whom hemolysis has not been optimally controlled by medical measures.

The exaggerated increase in platelets that follows removal of the spleen in agnogenic myeloid metaplasia is commonly associated with thrombotic or hemorrhagic phenomena, or both. The pathogenesis of the thrombotic phenomena in association with thrombocytosis is readily understood. The apparent paradox of an associated hemorrhagic diathesis requires further study. The theory that the bleeding is due to vascular fragility caused by local thrombotic injury is unsatisfactory. Bigelow[4] in 1954 found the serum serotonin activity to be low in 6 thrombocythemics, all with platelet counts greater than 1,000,000 per c.mm., suggesting that bleeding in such patients may be due to impaired vasoconstriction. Hardisty and Wolff[16] who found normal whole blood serotonin values but low mean platelet serotonin concentrations believe the platelets are not saturated with serotonin because of their increase in number. D'Antuano reported treatment of thrombocythemic patients with serotonin without any effect on their hemorrhagic status.

Spaet[36,37] demonstrated that the fundamental difficulty is a coagulation defect resulting from the anticoagulant effect of excess platelets. When in excess (over 2,000,000 per c.mm.), there is retardation of thromboplastin formation; when the platelets are diluted to normal, the thromboplastin generation is normal. Excess platelets also interfere with the thromboplastin already formed. Klein *et al.*[20] reproduced Spaet's experiments and added that the large number of platelets inhibit the action of thrombin and reduce the coagulability of fibrinogen. Larrieu, Caen and Bernard[24] also confirmed the work of Spaet. They suggest that the inhibitory effect of excess platelets is due to platelet lipid. Koller and Bounameaux[21] believe that there is a disproportion between the concentration of platelet Factor III (phospholipid) and the other clotting factors essential for thromboplastin formation. Miale and Garrett[30] were unable to reduplicate Spaet's work in the standard test but showed an inhibition of generation of thromboplastic activity in a dilute system (glass-stored, aluminum plasma) and serum. Marchal *et al.*[29] speak for the functional insufficiency of individual platelets, reflected by impaired generation of thromboplastin and thrombin, and an abnormal thromboelastograph in the pattern of bottle neck or "goulot de bouteille." Nelson and Stevenson[31] suggest the presence of both circulating and cellular anticoagulants.

In 2 of our patients some clotting factors were determined (Table 2). The only abnormality was that of a prolonged bleeding time in Case 1 with a normal fibrinogen value. Arlotti and Ballerini[2] proposed that the hemorrhages can be ascribed to a fibrinolysis secondary to microthrombi in the capillaries, which cause increased consumption of the prothrombin and fibrinogen; thus fibrinogen would be lost intravascularly. Levin, Celander and Gust[25] emphasize that lysis of platelets liberates sufficient platelet accelerator globulin and various other components of the thromboplastic system to produce rapid utilization of prothrombin and fibrinogen in the course of intravascular coagulation.

The diversity of recorded observations reflects on the complexity of the multiple factors involved in hemostasis. Certainly increased platelets appear to play an important role and the thrombotic or hemorrhagic phenomena, or both, may be relieved by reduction in the number of platelets toward normal by the administration of myelosuppressive agents. This is in keeping with the reports of Baikie, Cunningham and McAlpine[3], Fountain[13], Woodrow and Cope[39], Alajouanine *et al.*[1], Tubiana and Boiron[38], Laporte *et al.*[23], Coliez, Tubiana and Alagille[8], Gunz[15], and Ozer *et al.*[32] dealing with primary hemorrhagic thrombocythemia.

It is well known that ionizing radiation is capable of suppressing the activity of hemopoietic tissues. Radioactive phosphorus represents a method of semi-selective irradiation of hemopoietic tissue. Megakaryocytes are especially sensitive to ionizing radiation. In thrombocythemia the consequent reduction in the circulating platelets results in amelioration of the hemorrhagic or thrombotic tendencies, or both. Since the life span of platelets is short, the therapeutic effect of radioactive phosphorus is seen rather promptly. The effects may last for many months. In the event of relapse, retreatment is indicated.

Summary. 1) The clinical course of 6 patients with agnogenic myeloid metaplasia in whom splenectomy was followed by symptomatic thrombocythemia is reviewed.

2) Splenectomy may be indicated in agnogenic myeloid metaplasia complicated by hypersplenism which does not respond to medical measures such as steroid therapy and irradiation of the spleen.

3) Such indications, however, often fail to become apparent before debilitation precludes surgical intervention.

4) Thrombocythemia attended by hemorrhagic or thrombotic phenomena, or both, commonly follows splenectomy in agnogenic myeloid metaplasia.

5) In 5 of 6 patients, small doses of radioactive phosphorus controlled the thrombocythemia with amelioration of the hemorrhagic or thrombotic phenomena, or both.

6) The literature relative to the apparent paradox of thrombocythemia associated with hemorrhages is reviewed.

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SUMMARIO IN INTERLINGUA

Thrombocytosis: Un Complication Postsplenectomic in Myeloide Metaplasia Agnogene

1. Es revistate le curso clinic de 6 patientes con myeloide metaplasia agnogene in qui splenectomia esseva sequite de thrombocythemia symptomatic.

2. Splenectomia es indicate possibilemente in myeloide metaplasia agnogene complicate per hypersplenismo quando le condition non responde a mesuras medical como per exemplo un therapia steroide e irradiation del splen.

3. Tamen, tal indicationes, in multe casos, non deveni apparente ante que un stadio de debilitation es attingite le qual prohibi omne intervention chirurgic.

4. Thrombocythemia, associate con phenomenos hemorrhagic o thrombotic o ambes, seque communmente le effectuation de splenectomia in casos de myeloide metaplasia agnogene.

5. In 5 ex 6 patientes, le administration de micre doses de phosphoro radioactive reprimeva le thrombocythemia e resultava in un melioration del phenomenos hemorrhagic e/o thrombotic.

6. Es revistate le litteratura concernite con le apparente paradoxo de thrombocythemia associate con hemorrhagias.

A COMPARISON OF THE EFFECTIVENESS OF PENTAERYTHRITOL TETRANITRATE WITH PENTAERYTHRITOL TETRANITRATE AND MEPROBAMATE IN ANGINA PECTORIS

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It is well known that intense emotional reactions increase the demands on the heart and on the coronary circulation (Eskwith[3], Kowal[5], Weiss *et al.*[10]). With the advent of the tranquilizing drugs, an attempt has been made to reduce such demands on the heart by relieving emotional stress (Chevalier and Simon[1], Deitz[2], Eskwith[3], Shapiro[8], Snow[9]). Not only does this reduce the incidence of attacks of angina pectoris but it also helps alleviate the apprehension created by these episodes. Thus, it was suggested that the addition of the tranquilizer, meprobamate, to the vasodilator, pentaerythritol tetranitrate, might control angina more effectively than pentaerythritol tetranitrate alone.

However, the evaluation of therapy for angina pectoris is hazardous because of the subjective nature of the condition. Many forms of treatment have been heralded as therapeutic triumphs, only to be found useless by careful and prolonged observation (Katz[4]). The use of the double blind technique, together with the Master two-step (Master, Friedman and Dack[6]) test as a more objective measure of coronary adequacy, offers a relatively reliable method of evaluating the drug therapy of angina pectoris.

The present study concerns the use of this technique in a comparison between pentaerythritol tetranitrate alone, and pentaerythritol tetranitrate with meprobamate† on patients with angina pectoris.

Method. Patients, who fulfilled three diagnostic criteria, were selected for this study from the Clinic of The Long Island College Hospital: 1) each patient must have some objective evidence of arteriosclerotic heart disease, aortic stenosis, or aortic insufficiency; 2) each patient must have typical precordial pain, with or without radiation to the arms or neck, brought on by exertion or excitement and relieved by rest; 3) each patient must

*This investigation was carried out during the period when Doctor Younger was Chief Resident and Doctors DiPillo, Hoffman and Yarvis were Assistant Residents in the Department of Internal Medicine at the Long Island College Hospital.

†Equanitrate provided by Wyeth Laboratories, Philadelphia, Pa.

experience episodes of angina at least twice a week.

The study was divided into 2 periods of 4 weeks each. The two medications, pentaerythritol tetranitrate, 10 mg., and pentaerythritol tetranitrate 10 mg., with meprobamate, 200 mg., are to be referred to hereinafter, as PETN and PETN-M, respectively. They were supplied in identical capsules, packaged in identical bottles, one bottle for each 4-week period. The sequence of the bottles was randomized, and the contents were unknown to the investigators and the patients.

On admission to this study, each patient had a complete physical examination, electrocardiogram and chest film. Blood pressure and pulse were recorded and a Master two-step test was performed on the first visit. The patient was given one bottle of medication and was told to take 2 tablets after each meal and at bedtime. A printed daily log was given to each patient on which he could record the amount of pain which he was experiencing. The patient returned for a second visit 2 weeks after the initial visit. At this time, the blood pressure and pulse were recorded, the daily log was obtained from the patient and the patient was asked about the severity of pain and the side effects which he had had during the 2-week period.

The patient was continued on the same medication for a second 2-week period. Then the log was studied, blood pressure and pulse were recorded and a Master two-step test was performed. Inquiry was again made into the severity of pain and the side effects that he had had during the past 2 weeks. At this time, the patient was given a second bottle of medication. He returned 2 weeks later for blood pressure and pulse recording, study of the log and interrogation concerning the severity of pain that he had noted. He was told to continue on this bottle of medication for a second 2 weeks, at which time he returned for his final examination. The log was studied and inquiry was again made about the amount of pain which he had experienced, his blood pressure and pulse were recorded and a final Master two-step test was performed. Side effects were noted.

Results. Thirty-six patients were obtained who fulfilled the diagnostic criteria for this study. There were 22 males and 14 females, ranging in age from 33 to 86 years. Table 1 shows the diagnoses in these cases. Twenty-six of the 36 patients who started the experiment completed it.

Of the 10 patients who did not complete the study, 4 of the patients stopped because of hospitalization for their heart disease, 4 stopped for unknown reasons, and 2 stopped because of side effects of the medication.

TABLE 1.

Diagnosis	*Number of Patients*
Arteriosclerotic heart disease	21
Hypertensive cardiovascular disease	5
Rheumatic heart disease—	
Aortic stenosis	2
Aortic insufficiency	1
Arteriosclerotic and hypertensive heart disease	4
Rheumatic and hypertensive heart disease	3

A majority of patients reported a good response to both pentaerythritol tetranitrate (PETN) and the combination of pentaerythritol tetranitrate and meprobamate (PETN-M). Irrespective of the medication, there were 30 good response periods, 15 fair response periods and 17 poor response periods. Seventeen patients reported a good response to PETN-M, and 13 patients reported a good response period to PETN. Five patients reported a fair response to PETN-M, whereas 10 patients reported a fair response to PETN. Nine patients reported a poor response to PETN-M, and 8 patients reported a poor response to PETN.

If one compares the response of PETN-M with that of PETN in the same patient, one finds that 5 patients had a good but indistinguishable response to both medications, whereas 2 patients had a poor but indistinguishable response to both medications. Fifteen patients experienced a better re-

sponse to PETN-M than they did to PETN, although 2 of these patients reported a poor response to PETN-M and a very poor response to PETN. Eight patients had a better response to PETN than they did to PETN-M, one of whom reported a poor response to PETN and a very poor response to PETN-M. Ten of the 15 patients who reacted better to PETN-M, received the PETN-M last, whereas 6 of the 8 patients who responded better to PETN received the PETN last.

The results of the Master two-step test have been summarized in Table 2. The three tests were either entirely negative or entirely positive in 15 of 24 cases. Where there was a difference in the test between the two medication periods, the test was positive in the PETN period and negative in the PETN-M period in 7 cases. It was not positive in the PETN-M period and negative in the PETN period in any case.

Table 2 also permits a comparison

TABLE 2.—RELATION OF THE CLINICAL RESPONSE TO THE RESULTS OF THE MASTER TWO-STEP TEST.

	Master Two-step Test			*Clinical Response*	
No. of Cases	*Control*	*PETN*	*PETN-M*	*PETN*	*PETN-M*
3	Negative	Negative	Negative	Good	Good
3	"	"	"	Fair	Good
1	"	"	"	Good	Fair
2	"	"	"	Poor	Poor
1	"	Positive	"	Good	Good
1	"	"	"	Fair	Good
1	"	"	"	Fair	Fair
1	"	"	"	Poor	Fair
1	"	"	"	Poor	Poor
2	Negative	Positive	Positive	Good	Fair
1	Positive	Negative	Negative	Fair	Good
1	"	"	"	Good	Fair
1	Positive	Positive	Negative	Good	Good
1	"	"	"	Fair	Good
2	Positive	Positive	Positive	Good	Good
1	"	"	"	Fair	Good
1	"	"	"	Good	Poor
2	"	"	"	Poor	Poor

between the results of the Master two-step test and the clinical response to the two medications. It is evident from this data that there is no significant correlation between the results of the Master two-step test and the clinical response to the medications.

Fifteen patients experienced side effects from one medication or the other. Ten patients experienced side effects with PETN and 5 patients experienced side effects with PETN-M. Five patients complained of headaches, 5 complained of nausea, 3 complained of dizziness and one each complained of insomnia and drowziness. It is evident that all of these side effects, except drowziness, are those which are commonly encountered with PETN alone. Of the 2 patients who stopped their medication because of side effects, one experienced dizziness and palpitation and the other experienced anorexia and constipation.

Discussion. This double blind experiment was designed to test the difference in clinical effectiveness and the difference in the Master two-step test produced by pentaerythritol tetranitrate (PETN) as compared to pentaerythritol tetranitrate and meprobamate (PETN-M) in patients with angina pectoris. The results of the experiment indicate that there was little difference in either the clinical response or the results of the Master two-step tests.

It is evident from the results that PETN has some effect on angina pectoris, since the patients stated that they had a good response to one medication or the other, in 30 of 62 drug periods and a fair response in 15 drug periods.

The difference between the two medications is less evident. At first glance, there appears to be a better clinical response to PETN-M than to PETN alone. To wit; in 15 of the 30 patients in which clinical response comparison was possible, the response to PETN-M was better, whereas in only 8 of the 30 patients, the response to PETN was better. However, if one examines the order in which the drugs were administered, one finds that 16 of the 23 patients in whom there was a difference in response, found the second drug better than the first. Thus, 10 of the 15 patients who responded better to PETN-M received this drug second, while patients who responded better to PETN alone, received this drug second. Therefore, the difference in response is considerably less significant.

It is curious that the majority of patients responded better to the second medication rather than the first, as is usually the case. The explanation for this is not evident, unless possibly the patients were warming to their tasks and thought they were helping the examiners.

More than half of the patients showed no difference in the Master two-step tests from one medication period to the other. Only 7 of the 24 patients in whom the Master two-step tests were completed showed a better response to the PETN-M than to the PETN alone. Even though no patients showed a better response to PETN alone, the improvement in the 7 on PETN-M is not very impressive.

Incidentally, there was no trend in the Master two-step tests irrespective of medication. That is, a negative control Master two-step test was followed by a positive test at the end of the second medication period in only 4 patients, whereas a positive control Master two-step test was followed by a negative final test in only one case.

The side effects appear to be largely those related to the use of PETN. In some instances the use of meprobamate in addition to PETN appeared to prevent these side effects; at least the incidence of the side effects noted by

the patients taking PETN alone was higher than that noted by the patients taking the combination of drugs.

Although the results of this experiment are inconclusive, the use of the double blind technique with the Master two-step test demonstrates a relatively satisfactory method of evaluating the effectiveness of drugs for angina pectoris. It is interesting to note that Russek[7], performed a similar study using the double blind technique and the Master two-step test. His study differed, however, in two important respects. He used 2-week treatment periods and he selected for the Master two-step test only those patients whose control two-step test could be modified by sublingual nitroglycerine. Furthermore, his Master two-step tests were done in response to single doses of medication. Nevertheless, the differences which he noted in therapy with PETN as compared with PETN-M, were not significant either.

Summary. A double blind study has been made comparing the effectiveness of pentaerythritol tetranitrate (PETN) alone, with the effectiveness of pentaerythritol tetranitrate and meprobamate (PETN-M) in patients with angina pectoris.

Twenty-six of the 36 patients, who started the experiment, completed it. A majority of the patients reported a good response to both drugs.

A Master two-step test was performed in an effort to obtain a more objective evaluation of these drugs. The test was performed initially and then at the end of each medication period. Where there was a difference in the Master two-step tests between the two medication periods, the test was positive in the PETN period and negative in the PETN-M period in 7 cases. The reverse did not occur; that is, it was not positive in the PETN-M period and negative in the PETN period. However, when the clinical response in the two medication periods is compared with the results of the Master two-step tests, there is no essential difference.

Of the 15 patients who experienced side effects from the drugs, 10 experienced side effects on PETN alone, and 5 on the PETN-M.

The clinical results and the results of the Master two-step tests show such slight differences between the two medications as to be insignificant.

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SUMMARIO IN INTERLINGUA

Un Comparation de (1) Tetranitrato de Pentaerythritol con (2) Tetranitrato de Pentaerythritol e Meprobamato in le Tractamento de Angina de Pectore

Esseva effectuate un studio bis-occulte pro comparar le efficacia de tetranitrato de pentaerythritol (TNPE) con le efficacia de tetranitrato de pentaerythritol

e meprobamato (TNPE-M) in le tractamento de patientes con angina de pectore.

Vinti-sex del 36 patientes le quales comenciava le experimento completavo lo. Un majoritate del patientes reportava un bon responsa a ambe drogas.

Le test a duo scalones de Master esseva executate pro obtener un evalutation plus objective del drogas. Le test esseva executate primo al initio e postea al fin de cata un del periodos de medication. In tanto que il occurreva un differentia inter le tests a duo scalones de Master al un e al altere periodo de medication, le test esseva positive in le periodo de TNPE e negative in le periodo de TNPE-M in 7 casos. Le contrario non occurreva, i.e. le series includeva nulle caso in que le test esseva positive in le periodo de TNPE-M e negative in le periodo de TNPE. Tamen, si le responsa clinic in le duo periodos de medication es comparate con le resultatos del tests a duo scalones de Master, nulle differentia essential pote esser notate.

Ex le total de 15 patientes qui experientiava adverse effectos lateral como effecto del drogas, 10 experientiava los solmente con TNPE e 5 con TNPE-M.

Le resultatos clinic e le resultatos del test a duo scalones de Master revela, inter le duo medicationes, differentias talmente leve que on non pote considerar los como significative.

(Interlingua continued from page 95)

2. Evidentia de reducite requirimentos de insulina non esseva notate a ulle tempore in ullo de iste subjectos.

3. Hypertension esseva presente in 85% del casos.

4. Grados marcate de proteinuria esseva trovate uniformemente in omne le patientes.

5. Alterationes pathologic constatate in le insulas e in le glomerulos non poteva esser correlationate mutualmente. Similemente, nulle correlation esseva establibile inter le alterationes insular e le presentia o absentia de acidosis diabetic.

6. Le identification histologic de glomerulosclerosis nodular require stricte criterios, como illos esseva formulate per Kimmelstiel e Wilson.

NODULAR GLOMERULOSCLEROSIS: CLINICO-PATHOLOGICAL CORRELATION OF 40 ADVANCED CASES*

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The importance of nodular glomerulosclerosis as a pathognomonic lesion of diabetes mellitus has increased over the recent years since its description by Kimmelstiel and Wilson[10] in 1936. Many controversies have arisen with regard to interpretation, clinical significance, and histogenesis of the lesion. More specifically, it has been stated by some workers that when this lesion exists there is a diminished insulin requirement on the part of the patient, and rarely is there a recent or past history of clinical acidosis. In view of the report of Zubrod, Eversole and Dana[20] and the opposite view of Epstein and Zupa[3] and Runyan, Hurwitz and Robbins[17] we felt that a critical review of cases of advanced nodular glomerulosclerosis as seen in the files of Kings County Hospital from the years 1950 through 1959 would be of interest with regard to this question of diabetic nodular glomerulosclerosis and acidosis. During this period, 525 necropsies were performed on diabetic patients. Forty, or 7.6%, of the kidneys histologically examined proved to show specific findings of advanced nodular glomerulosclerosis. In this paper we concerned ourselves only with the advanced or grade III and IV lesions in nodular glomerulosclerosis. The method of grading is described below (Refer to Table 1).

TABLE 1.—METHOD OF CLASSIFYING KIMMELSTIEL WILSON KIDNEYS (Epstein and Zupa[3])

1 to 5 glomeruli per every 20 glomeruli counted having at least one nodule present is GRADE 1.
6 to 10 is GRADE 2.
11 to 15 is GRADE 3.
16 to 20 is GRADE 4.

In this series of 525 diabetic necropsies there were numerous instances of minimal to moderate involvement of glomeruli by the nodular lesions (grade I and II). The percentage incidence of nodular glomerulosclerosis found in our series (7.6%), is not in accord with the series of Warren and Le Compte[18] who found nodular glomerulosclerosis in 17% of diabetic necropsies. However, in their paper there was no attempt to distinguish minimal from marked or advanced involvement which may well explain this percentage difference. The percentage incidence of glomerulosclerosis in diabetics as reported by various authors is seen in

*This investigation was supported by research grant No. A-2105, National Institutes of Health, Public Health Service.

Table 2. In addition to evaluating the incidence of acidosis in diabetic nodular glomerulosclerosis, an attempt is made to correlate the presence and degree of damage with the islet cell changes in the pancreas in these cases.

Amongst the lesions seen in the glomerulus in the diabetic patient are included a diffuse intercapillary change known as diffuse intercapillary glomerulosclerosis, and hyaline or "exudative" sudanophilic nodules located in an extracapillary position (Fig. 1). The latter are not infrequently found in Bow-

TABLE 2.—INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETICS AS REPORTED BY VARIOUS AUTHORS SINCE 1941

Author	Year	No. of Cases of Diabetes	No. of Cases of Glomerulosclerosis*			Percentage Incidence of Intercapillary Glomerulosclerosis	No. and Percentage of These Cases Considered Advanced or Severe†	
			I	II	III		No.	%
1. Allen and Siegal	(1941)	105		35		33	10	9.5
2. Horn and Smetana	(1942)	144	33			22.9	—	—
3. Laipply *et al.*	(1944)	124	79			63.7	29	23.4
4. Goodof	(1945)	214	94			44	20	9.3
5. Henderson *et al.*	(1947)	313	61			19.5	30	9.6
6. Kimmelstiel and Porter	(1948)	—	—	—	—	17	—	—
7. Zins	(1949)	50	41			82	—	—
8. Harman	(1950)	116	34			29.3	—	—
9. Zubrod *et al.*	(1951)	178	41			23	4	8
10. Hall	(1952)	120		45		37.5	14	11.7
11. Rogers *et al.*	(1952)	387		100		26	55	14.2
12. Bell	(1953)	1465		239		16.3	—	—
					367	25	—	—
13. Reid	(1955)	104		26		25	—	—
14. Lambie and Macfarlane	(1955)	120		55		46	23	19.2
15. Runyan *et al.*	(1955)	375	138			37	—	—
16. Epstein and Zupa	(1956)	137		37		27	25	18.3
17. Hennigar *et al.*	(1960)	525		40		7.6	40	7.6

*I—No distinction made between nodular and diffuse glomerulosclerosis.
II—Nodular glomerulosclerosis specified.
III—Total sum of the cases specified as nodular or diffuse glomerulosclerosis.
† Those cases considered as advanced or severe by the respective authors according to their own criteria.

Material and Methods. It appeared extremely important to establish criteria for the histological identification of the lesions in the context in which they were described by Kimmelstiel and Wilson. There has been considerable confusion in the histological interpretation of diabetic glomerulonephropathy.

man's capsule as well as the glomerular tufts. Also seen are large circular vacuoles or fatty material not associated with any of the previous mentioned lesions. Rarely, calcification of fatty materials is evident. Concentric laminated fibrosis emanating from Bowman's capsule and obliterating Bowman's space is often

accompanied by glomerular fibrosis with eventual obsolescence. One rarely encounters features manifested by necrosis found in malignant hypertension. Glomerulonephritis and amyloid deposits are rarely demonstrated.

Lastly, the lesions with which this paper is concerned are those described by Kimmelstiel and Wilson and consist of a collagenized or fibrous reticulated silver-positive, slightly cellular nodule occurring in the intercapillary space. Here and there one sometimes sees fatty vacuoles within this "hard" nodule.

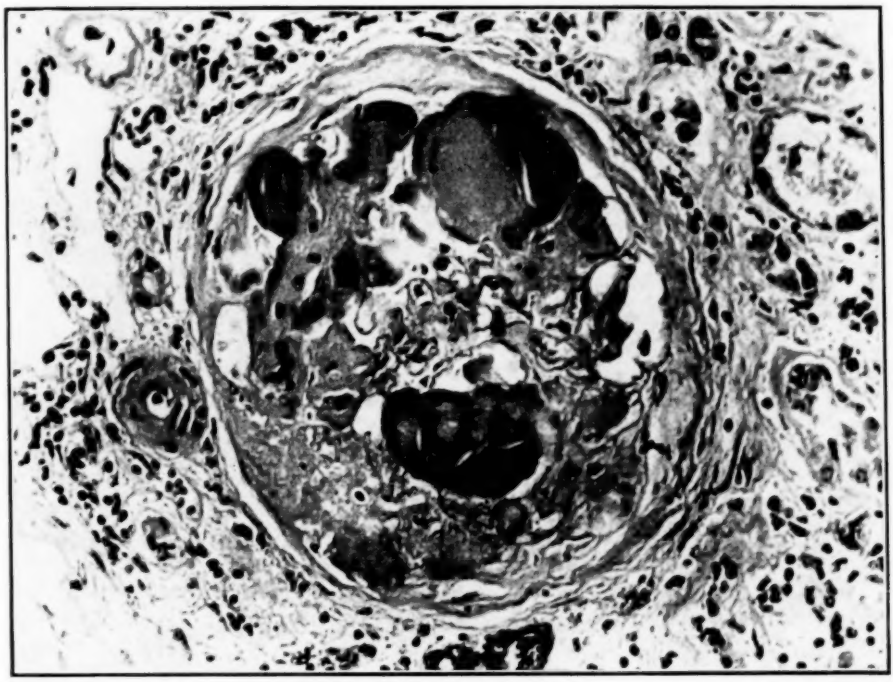

Fig. 1.—"Exudative" nodules often mistaken for nodular glomerulosclerosis (× 150).

The capillaries at the periphery of the nodule are dilated and prominent and are usually thin walled. In the majority of cases of diabetic glomerulonephropathy, it would appear that the nodular lesion is the end result of advancing diffuse intercapillary glomerulosclerosis. On the other hand, a nodular lesion may be seen in the absence of, or, when there is, minimal diffuse intercapillary change. Occasionally, one encounters a glomerulus which shows the presence of one large nodule occupying almost the entire structure. Confluence of the nodules leads to obsolescence of the glomerulus.

Since it is clear that both advanced diffuse intercapillary glomerulosclerosis and advanced nodular glomerulosclerosis can result in the nephrotic syndrome, it seems important that the concept of clinical nephrosis and the morphologic concept of nodular glomerulosclerosis not be used interchangeably.

Two to 10 histological sections of kidneys were available on the cases. Numerous staining procedures were used to study the kidney sections and these included hematoxylin and eosin, oil red O, Masson trichrome, Verhoff Van Gieson, PAS, Alcian blue, colloidal iron Alcian blue (according to the method of Muller and Mowry), Wilder reticulum and PAS-Wilder reticulum.

The criteria for hypertension were those of a past history of hypertension and a blood pressure of over 140/90 or a heart weight of greater than 400 gm. in the absence of valvular heart disease.

An examination of the clinical records for the presence of acidosis was executed. The criteria for the establishment of clinical acidosis was either a history of diabetic coma,

ketonuria, or diminished carbon dioxide combining power.

Results. These findings reveal that of the 40 patients with advanced or grade III and IV nodular glomerulosclerosis 19 patients, or 47.5%, showed positive evidence of acidosis. Of the 19 patients with diabetic acidosis and nodular glomerulosclerosis 15 showed no lesions in the islet cells of the pancreas. Of the remaining 21 patients without evidence of diabetic acidosis, 12 showed islets free of pathological changes. Of the 19 patients with diabetic acidosis, 4 showed hyalinization of the islets. On the other hand, in

TABLE 3.—SUMMARY OF CLINICAL AND PATHOLOGICAL FINDINGS

Case	*Grade of Nephropathy*	*Average No. of Nodules per Glomerulus*	*Clinical Acidosis*	*Hypertension*	*Pancreatic Pathology*
1	IV	3.3	−	+	+
2	IV	3.1	+	+	−
3	III	1.6	−	+	+
4	IV	4.2	−	+	−
5	IV	2.4	+	+	+
6	IV	2 2	+	+	−
7	III	2.7	−	−	+
8	IV	3.2	+	+	+
9	IV	3.5	+	+	−
10	IV	1.9	+	+	+
11	IV	2.3	−	+	−
12	IV	4.2	−	+	+
13	III	1.6	−	+	+
14	III	2.5	+	+	−
15	IV	3.1	−	+	−
16	III	2.8	+	+	−
17	IV	4.2	−	−	−
18	III	2.6	−	−	+
19	III	2.4	+	+	−
20	IV	4.3	−	+	−
21	IV	3.6	+	+	−
22	IV	3.2	−	−	−
23	III	4.0	+	+	−
24	IV	2.7	+	+	−
25	IV	2.4	+	+	−
26	III	2.1	+	+	+
27	III	3 2	+	+	−
28	IV	2.7	−	+	+
29	III	2.9	−	−	+
30	IV	4.6	−	+	−
31	IV	4.1	+	+	−
32	III	1.3	+	+	−
33	IV	2.6	−	+	−
34	IV	2.9	−	+	−
35	IV	4.6	−	+	+
36	III	3.2	−	+	−
37	IV	5.7	−	+	−
38	III	2.8	+	+	+
39	III	2.5	−	−	−
40	III	2.1	+	+	−
%	IV = 60% Avg. −3.03 III = 40%		47.5%	85%	35%

the nonacidotic group of 21 patients, 9 revealed hyalinization. Thus of the 40 cases, 26 prove to have completely normal histological sections of the pancreas (Table 3).

All 40 cases showed the classical triad of edema, massive proteinuria, and hypoalbuminemia. In addition, 85% proved to have significant degrees of hypertension.

Also, in reviewing the cases, there was no evidence of decreased insulin requirements as an indication of amelioration of the diabetes at any time during the patient's life.

Discussion. In recent years several articles dealing with the rarity of acidosis, amelioration of diabetes and decreased insulin requirements in patients with Kimmelstiel-Wilson disease have appeared in the literature. Zubrod, Eversole and Dana[20] state: "The virtual absence of acidosis throughout the entire duration of diabetes in patients with Kimmelstiel-Wilson lesions has not been described previously. This rarity of diabetic acidosis is so striking that it provides a clue during life to the presence of Kimmelstiel-Wilson lesions and suggests a metabolic variation from ordinary diabetes." On the other hand, Runyan, Hurwitz and Robbins[17] state: "There is no evidence in this study to support the thesis of Zubrod, Eversole, and Dana that a specific type of diabetes, characterized by amelioration of the severity of the disease and infrequent occurrence of acidosis is associated with Kimmelstiel-Wilson renal lesions *per se*." Epstein and Zupa[3] state: "The present study does not support the view that a specific or unique type of diabetes, characterized by infrequent episodes of acidosis and a decreasing requirement of insulin is associated with the nodular glomerular lesion of Kimmelstiel and Wilson." Rifkin[15] states: "The amelioration of diabetes as the renal lesion progresses, and the rarity of acidosis in the course of the diabetic patient's life-time was first pointed out by Zubrod and his associates of the Johns Hopkins Hospital. This has since been challenged by many clinicians who have large numbers of such diabetic patients under their care. While it is true that many patients with diabetic glomerulosclerosis tend to develop a diminished insulin requirement as the disease progresses, similar signs can be observed in diabetics who develop a wide variety of other nonspecific renal diseases. The more likely explanation would appear to be a marked diminution of caloric intake, rather than a specific metabolic disturbance."

We believe that this study points up some interesting observations. Firstly, it is clear that many investigators have not strictly adhered to the morphological criteria of Kimmelstiel and Wilson in their evaluation and interpretation of the lesion known as nodular glomerulosclerosis. One sees the hyaline sudanophilic nodule, depicted in microphotographs and articles, referred to as nodular glomerulosclerosis (Fig. 1). One also encounters microphotographs of advanced diffuse intercapillary glomerulosclerosis with some prominence of the intercapillary material (Fig. 2), being incorrectly referred to as the lesion of nodular glomerulosclerosis. Many pathologists have been content to find a scattered nodule here and there in glomeruli and designate the kidney as nodular glomerulosclerosis. We feel that if the lesions are not of Grade III or Grade IV intensity (Fig. 3), they probably have little significance with reference to disturbances in the physiological role of the glomerulus. Secondly, it is obvious that by the time the glomerulus shows Grade III or Grade IV lesions there is tubular atrophy, retention of urea nitrogen, and in the majority of

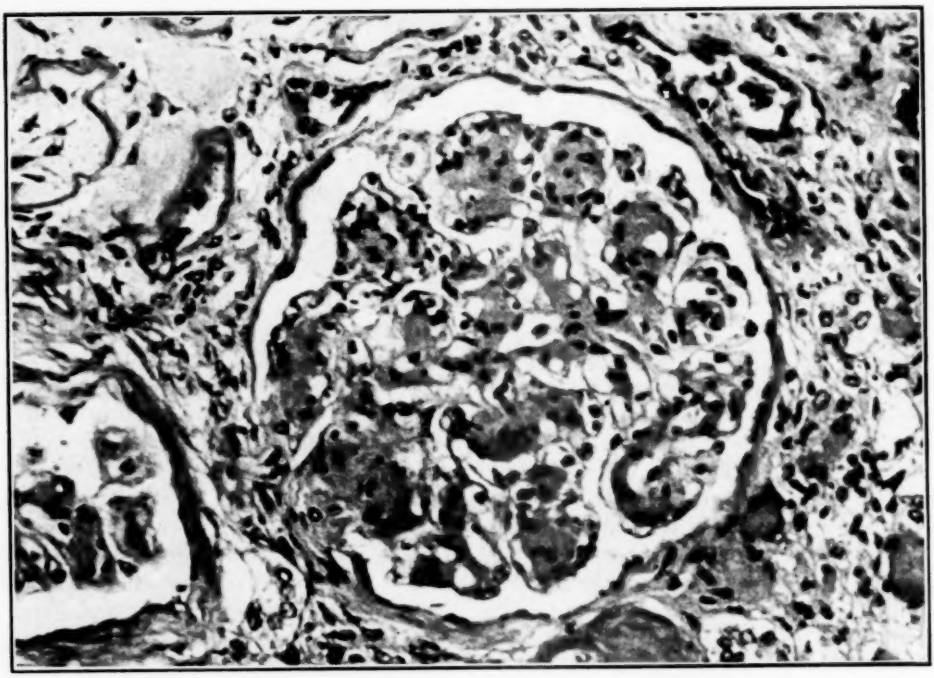

Fig. 2.—Diffuse intercapillary glomerulosclerosis simulating the nodular form (× 170).

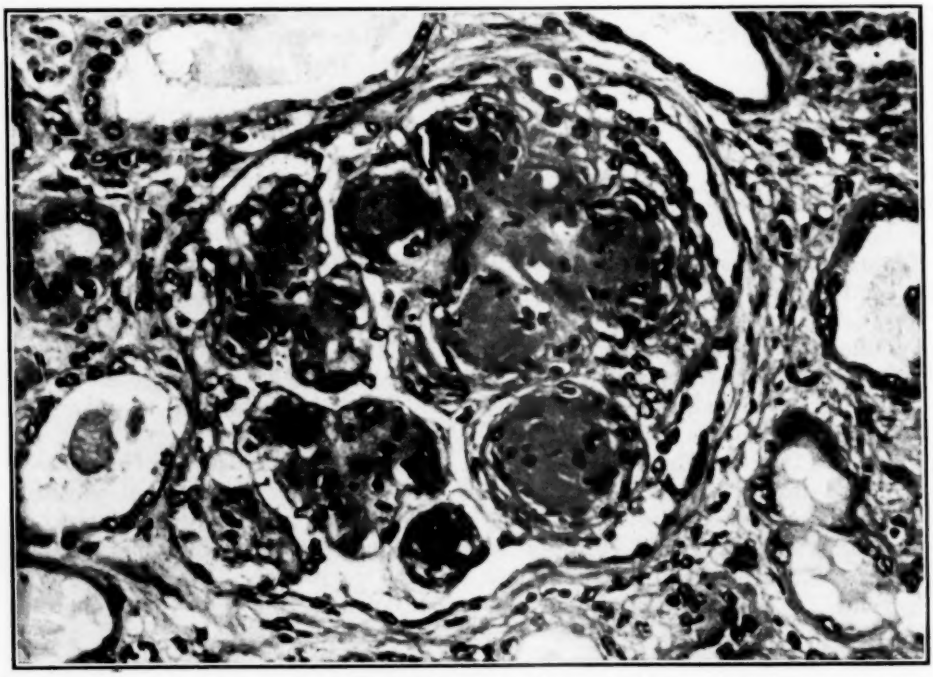

Fig. 3.—Glomerulus from a case of Grade IV nodular glomerulosclerosis, depicting the classical advanced Kimmelstiel-Wilson lesion (× 170).

cases hypertension has appeared. In this series, hypertension was present in 85% of the cases. No correlation between minimal to marked changes in the islets could be made with the glomerular changes. Lastly, it is clear that the development of advanced nodular glomerulosclerosis in no way protects the patient from the development of acidosis. In the entire series of 40 cases, a marked degree of proteinuria (3+ to 4+) was demonstrated. On the other hand, experience clearly points to diffuse intercapillary glomerulosclerosis without nodular lesions as a cause of the clinical nephrotic syndrome. In our study it was the advanced nodular type of glomerulosclerosis which consistently resulted in massive proteinuria.

Summary. 1. In a series of 40 cases of advanced (Grade III and IV) diabetic nodular glomerulosclerosis, 19 patients had a history of diabetic acidosis.

2. At no time was there evidence of a diminished insulin requirement in these patients.

3. Hypertension was present in 85% of the cases.

4. Marked proteinuria was consistently found in all of the patients.

5. Pathologic changes in the islets could not be correlated with those seen in the glomeruli, nor were they related to the presence or absence of diabetic acidosis.

6. The histological identification of nodular glomerulosclerosis requires strict criteria as laid down by Kimmelstiel and Wilson.

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SUMMARIO IN INTERLINGUA

Glomerulosclerosis Nodular: Correlation Clinico-Pathologic in 40 Avantiate Casos

1. In un serie de 40 casos de avantiate glomerulosclerosis nodular diabetic (grados III e IV), 19 concerneva patientes con un anamnese de acidosis diabetic.

(Interlingua continued on page 88)

THE EFFECT OF PROBENECID ADMINISTRATION ON BLOOD LIPIDS AND LIPID TOLERANCE CURVES IN SUBJECTS WITH MYOCARDIAL INFARCTION*

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It has long been known that individuals with gout, a primary disorder of uric acid metabolism, manifest a high incidence of vascular complications (coronary, cerebral and peripheral) (Diamond[9], Duncan[11], Trout *et al.*[29], Upmark and Adner[31]). Likewise, it has been found that subjects with evidence of arteriosclerosis have higher levels of uric acid in their blood than normal controls (Dreyfus and Czaczkes[10], Gertler, Garn and Levine[13], Gertler and White[15], Kahn and Prozan[20], Kramer, Perlstein, and DeMadeiros[22], Storti[28]). The exact relationship between abnormal uric acid metabolism and vascular disease, however, is still not definitely known. Further, there is increasing evidence that coronary artery disease is related to alterations in lipid balance and metabolism, and this may become clinically evident by the presence of abnormal serum lipid concentrations or abnormal fat tolerance curves (Barret[4], Seller *et al.*[26]).

With these facts in mind, the present study was undertaken to determine the effect on blood lipids of increasing uric acid excretion by the administration of probenecid in subjects with myocardial infarction. In order to obtain a complete picture of the influence of lowered blood uric acid levels on lipid handling, effects on radioactive fat tolerance curves as well as on serum lipid concentrations were studied. If lipid patterns could be modified by this means, a possible new therapeutic approach would be made available in the control of coronary artery disease.

Material and Methods. Ten patients with myocardial infarction proven by history, physical examination, electrocardiogram and other laboratory tests were selected from the wards of the Philadelphia General Hospital. Four patients were convalescing from an acute myocardial infarction and 6 had suffered an infarction in the past. Patients with diabetes or congestive heart failure, or both, were excluded since it has been observed that in these conditions low fat tolerance levels are obtained (Hakkela, Makela and Haloren[18], Sandberg *et al.*[24]). Drugs which might inter-

*This work was aided by a grant from the U.S. Public Health Service (Grant H141, C-8).

fere with the action of probenecid or compete with it, such as penicillin, sulfonamides, large doses of aspirin, para-aminosalicylic acid, Diodrast, and the like, were avoided (Beckman[5], Goodman and Gilman[16]).

Baseline determinations of serum uric acid by the method of Brown[8], serum cholesterol by the method of Abell and associates[1], serum triglycerides by the method of Van Handel and Zilversmit[32], serum phospholipids by the method of Youngburg and Youngburg[33] and lipid tolerance curves by the method of Beres, Wenger and Kirsner[5] were obtained in all subjects studied. Probenecid, in a daily dose of 1.5 gm., was then administered until a significant fall in serum uric acid was noted (about 2 or 3 weeks), and the lipid determinations and tolerance curves were then repeated. An attempt was made to keep the diet as relatively fixed in lipid and purine content as possible. Although some subjects had received heparin, in all instances this was discontinued several days prior to the control lipid studies.

Results. Table 1 lists the normal values for our laboratory. In the I_{131} triolein curve table it will be noted that we have set two standard deviations above the mean as the upper limit of normal. By so doing, we have found that false positives are not obtained. However, frequent cases of myocardial infarction will fall between one and two standard deviations above the mean.

Table 2 contains the serum lipid values and radioactivity data of all the experiments performed. The following results were obtained:

SERUM URIC ACID. In all cases there was a significant fall in serum uric acid after probenecid. The mean reduction in uric acid level was 2.3 mg. per 100 ml. The control uric acid was abnormally high in 4 of the 10 subjects.

SERUM CHOLESTEROL. There was a significant drop in cholesterol concentration after probenecid in only one subject. This patient had an abnormally high control cholesterol. One subject showed a cholesterol rise after the drug.

TABLE 1.—NORMAL VALUES

Serum Lipids	*(mg. per 100 ml.)*		*I_{131} Triolein Curve**	
			Mean ± S.D.	Mean + 2 S.D.
Cholesterol	to 240			
Lipid Phosphorus	8.5–11.5	WBP	11 ± 3.5	17.9
Triglycerides	25–150	TCAP	4.5 ± 1.5	7.4
Uric Acid (M)	to 6.0	WB^{24}	2.9 ± 1.5	5.8
Uric Acid (F)	to 5.0	TCA^{24}	0.6 ± 0.37	1.4

*Radioactivity expressed as percentage of ingested dose.

M = Male
F = Female
WBP = Peak radioactivity of the whole blood.
TCAP = Peak radioactivity of the fraction of blood precipitated by trichloracetic acid.
WB^{24} = Radioactivity of the whole blood at the end of 24 hours.
TCA^{24} = Radioactivity of the fraction of blood precipitated by trichloracetic acid at the end of 24 hours.

SERUM TRIGLYCERIDES. No significant changes were noted after probenecid.

SERUM LIPID PHOSPHORUS. Significant elevations occurred in 3 subjects after probenecid.

I_{131} TRIOLEIN CURVES. One case, whose control curve was between 1 and 2 standard deviations above the mean, showed a fall after probenecid.

It can be noted that we found a fairly high incidence of hyperuricemia (40%) in our subjects, all of whom had experienced a myocardial infarction. In each case we obtained a significant fall in the uric acid levels after probenecid, yet there was a fall in serum lipid levels and in the I_{131} triolein curves in only 2 instances. It is noteworthy that

TABLE 2.—THE EFFECT OF PROBENECID ON SERUM LIPID VALUES AND ON FAT TOLERANCE CURVES

Patient	Experiment	Uric Acid (mg./100 ml.)	Cholesterol (mg./100 ml.)	Triglycerides (mg./100 ml.)	Lipid Phosphorus mg./100 ml.)	I_{131} Triolein Curve*					
						Type	2 hrs.	4 hrs.	6 hrs.	8 hrs.	24 hrs
						WB	2.45	13.67	14.40	10.71	3.38
C.C. 46 M	A.	6.3	146	100.4	9.8	TCA	0.30	3.48	5.43	2.06	0.24
						WB	8.2	14.39	12.47	9.70	2.33
	B.	3.5	210	95.7	9.5	TCA	1.43	6.42	4.67	2.39	0.11
						WB	2.85	14.14	12.46	10.72	5.51
R.A. 57 M	A.	5.4	219	114.4	10.0	TCA	3.49	4.10	2.15	1.66	0.47
						WB	4.66	11.00	14.74	10.66	4.73
	B.	2.0	238	113.9	10.0	TCA	0.93	4.10	7.17	2.70	0.42
						WB	7.10	12.64	10.30	5.78	2.27
A.F. 57 M	A.	5.5	216	91.9	9.8	TCA	2.55	6.75	5.24	1.44	0.23
						WB	2.63	9.41	9.44	7.86	
	B.	3.3	246	117.7	9.4	TCA	0.60	3.55	3.55	2.45	
						WB	4.37	11.11	10.17	8.77	4.87
G.G. 75 M	A.	3.4	176	86.6	10.0	TCA	0.73	4.22	3.16	1.52	0.31
						WB	3.50	9.07	11.55	8.86	3.61
	B.	2.4	176	107.5	9.7	TCA	0.79	2.76	4.53	2.11	0.51
						WB	0.56	7.80	12.60		6.89
W.W. 58 M	A.	6.3	390	112.8	10.4	TCA	0.15	2.61	7.66		0.81
						WB	3.06	4.04	21.94	16.65	
	B.	3.6	314	118.3	10.1	TCA	0.00	0.99	12.31	8.72	

	B.	3.6	314	118.3	10.1	TCA	0.00	0.99	12.31	8.72	
R.B. 65 F	A.	6.3	166	74.0	7.8	WB	0.75		4.77	9.83	7.55
						TCA	0.38		2.61	5.61	0.76
	B.	3.0	144	72.7	16.0	WB	4.40	13.82	17.06	10.85	
						TCA	0.46	3.55	6.81	2.43	
J.L. 70 M	A.	5.7	136	74.6	5.6	WB	2.26	9.84	11.93	9.17	5.63
						TCA	0.80	4.34	5.51	1.57	0.35
	B.	4.2	152	27.2	9.2	WB	0.46	4.35	10.86	11.80	
						TCA	0.00	0.93	3.96	3.77	
B.W. 48 F	A.	4.9	243	58.0	10.2	WB		16.86	14.14	8.39	2.74
						TCA		7.88	6.48	1.96	0.34
	B.	3.0	242	56.3	12.3	WB	6.10	9.28	13.43	15.09	6.45
						TCA	0.73	1.40	4.84	7.66	0.79
W.K. 37 M	A.	6.3	168	90.4	9.1	WB	0.81	6.93	12.95	8.30	3.30
						TCA	0.25	3.03	6.27	2.22	0.36
	B.	2.8	152	119.4	11.5	WB	2.59	13.81	16.26	11.60	
						TCA	0.3	4.75	6.59	3.08	
P.R. 54 F	A.	4.8	254	60.4	10.2	WB	4.45	15.93	14.20	12.57	7.13
						TCA	0.53	5.36	4.29	4.88	0.28
	B.	4.0	245	84.8	10.3	WB	1.79	10.86	13.35	11.98	6.44
						TCA	0.21	2.62	4.50	2.47	0.34

M = Male
F = Female

A. = Before probenecid
B. = After probenecid
WB = Whole blood
TCA = Fraction of blood precipitated by trichloracetic acid.

*Radioactivity expressed as percentage of ingested dose.

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the I_{131} triolein curves were reproducible in every patient after a 2- to 3-week interval, when one considers the many factors which must influence it. Our incidence of abnormal I_{131} triolein curves was not as high as in the myocardial infarction series of Seller and associates[26]. This may be due to the fact that 3 of our cases were over 60 years of age. It has been noted that if older individuals have a marked impairment of fat absorption, a low oral fat tolerance curve will be found even in the presence of myocardial infarction (Unpublished observations[30]).

Discussion. The coexistence of vascular disorders and a derangement of fat and uric acid metabolism have been noted by many investigators (Diamond[9], Dreyfus and Czaczkes[10], Duncan[11], Gertler, Garn and Levine[13], Gertler and White[15], Kahn and Prozan[20], Kramer, Perlstein and DeMadeiros[22], Storti[28], Trout *et al.*[29], Upmark and Adner[31]). One of the chief complications of gout is arteriosclerosis (Diamond[9], Duncan[11], Trout *et al.*[29]). Likewise, it has been shown that subjects with coronary artery or peripheral vascular disease, or both, have higher levels of blood uric acid than normal controls (Dreyfus and Czaczkes[10], Gertler, Garn and Levine[13], Gertler and White[15], Kahn and Prozan[20], Kramer, Perlstein and DeMadeiros[22], Storti[28], Upmark and Adner[31]). Gertler and Oppenheimer[14] and Praetorius[23] showed that this is not a manifestation of age or sex differences. The series of normals studied by Gertler and Oppenheimer showed a slightly higher level of uric acid in the male, but no appreciable rise with age.

As far as has been demonstrated, there is no interrelationship or common precursor in the intermediate metabolism of fat and uric acid (Adlersberg[2], Duncan[11], Gutman *et al.*[17], Seigmiller and Laster[25]). However, it has been shown that uric acid excretion can be decreased by feeding a high fat diet (Adlersberg[2], Adlersberg and Ellenberg[3]). Also, there is a higher incidence of hyperuricemia in individuals with familial hypercholesterolemia (Adlersberg[2], Fulton[12], Harris-Jones[19], Kahn and Prozan[20]). It is postulated that since gout and familial hypercholesterolemia are inherited inborn errors of metabolism, the genes controlling these might be similarly located, and consequently, more apt to occur together (Adlersberg[2], Fulton[12], Kahn and Prozan[20]). In fact, where they occur together, the degree of abnormality of each appears to be of the same magnitude (Adlersberg[2], Harris-Jones[19], Kahn and Prozan[20]).

An entirely different relationship was postulated by Trout and associates[29] as a result of postmortem findings in 2 cases of gout. They found urate crystals in vascular thrombi and atheromatous plaques, and felt that the coexistence of these two disorders might be due to the following mechanisms: (1) Urates increase coagulability of blood and cause clotting. (2) Urates act as surface active agents enabling cholesterol to fix itself to the vascular wall.

The relationship between disorders of lipid and uric acid metabolism and coronary artery disease was first properly appreciated in 1928 by Bridges who used aspirin as a uricosuric agent and hoped to improve the severity of angina in a series of his patients with gout[7]. He noted significant symptomatic improvement in these patients, but it is possible that this was simply an analgesic effect. In 1959 Kahn and Prozan[20] discussed the possibility of uricosuric drugs in the treatment of coronary artery disease.

Probenecid is an effective oral uricosuric agent which blocks tubular reabsorption of urates (Beckman[5], Goodman and Gilman[16]). It is believed that

this is done by inhibiting the formation of "active urate" necessary for tubular transport (Goodman and Gilman[16], Sirota, Yu and Gutman[27]). The dosage schedule that we used was almost the maximum therapeutic dose recommended (Beckman[5], Goodman and Gilman[16]). With this dose we were able significantly to lower the uric acid levels in the blood. Yet, in almost all instances, no significant reduction in blood lipid levels or in fat tolerance curves resulted. This would seem to indicate that elevated uric acid levels are not the cause of the abnormal lipid patterns when these are shown to coexist with hyperuricemia in patients with coronary artery disease. In a previous study from our laboratory[21] it was shown that when pyrazinamide was given to patients a marked hyperuricemia developed, and yet no significant change in blood lipids resulted.

Perhaps long term therapy with a uricosuric agent in patients with coronary artery disease who are found to have elevated blood uric acid levels may help to shed more light on this problem.

Summary. Probenecid, as a uricosuric agent, was given to 10 patients with myocardial infarction, 4 of whom had hyperuricemia, to determine whether the lipid patterns in these cases would change as the uric acid levels fell. A definite decline of serum uric acid was obtained in each, but this was not associated with any significant group alteration of lipid patterns in short term experiments.

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SUMMARIO IN INTERLINGUA

Le Effecto del Administration de Probenecida Super le Lipidos Sanguinee e le Curvas del Tolerantia pro Lipidos in Subjectos con Infarcimento Myocardial

Probenecida, como agente uricosuric, esseva administrate a 10 patientes con infarcimento myocardial (incluse 4 con hyperuricemia) pro determinar si le configurationes lipidic se alterarea in iste casos in concomitantia con le declino del nivellos de acido uric. Un definite declino del nivellos seral de acido uric esseva obtenite in omne le casos, sed iste evento non esseva associate, pro le gruppo total, con ulle significative alteration del configuration lipidic. Es a notar que le experimentos esseva experimentos a curte vista.

A CONTROLLED STUDY OF CODEINE, DEXTRO PROPOXYPHENE AND RO 4-1778/1

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Codeine is a useful analgesic, but it has at least four limitations. It is an addicting drug, the raw material necessary for its manufacture may not always be available to the Western World, there are many patients who experience undesirable side effects from its use, and it has limited value in severe visceral pain. Dextro propoxyphene and ethoheptazine are important new drugs because they are synthetics, they are not classified as addicting agents, and they cause fewer undesirable reactions. In spite of these developments, there still is a need for effective analgesics which are at least as potent as codeine and which are free of the limiting characteristics of the narcotics. It appears that a recently synthesized compound, Ro 4-1778/1, may meet these requirements. This drug was described first by Brossi *et al.*[1]. Chemically it is 1(p-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and thus belongs to a new chemical group of analgesics. The structural formula of Ro 4-1778/1 is shown in Fig. 1.

In preliminary clinical trials[2] we found that the analgesic effectiveness of Ro 4-1778/1 and of codeine, milligram for milligram, is of the same order if these drugs are given orally. The purpose of the present study was to expand our knowledge of the clinical characteristics of Ro 4-1778/1, especially in comparison with other agents. To accomplish this, we selected a group of patients from the postsurgical orthopedic wards who were hospitalized for some period of time and had a rather consistent requirement for oral analgesics of the potency of codeine. These patients had the same general type of skeletal-muscular pain. This uniformity is an advantage when one is testing different analgesic drugs and dosages. In designing a clinical study of this kind it was considered advantageous to use two doses each of a standard analgesic drug, codeine; a more recently accepted analgesic drug, dextro propoxyphene; the experimental analgesic; and a placebo for control purposes.

Procedures. Forty-three male patients were included in the study. Pain before drug administration was graded as 3, severe; 2, moderate; and 1, slight. The average intensity of premedication pain for all patients was 1.8 (moderate to slight), that is sufficiently severe to warrant the use of at least 30 mg. codeine orally. Our earlier studies had shown that a statistically significant analgesic effect was obtained 90 minutes after oral administration of codeine. Postmedication observations were, therefore, limited to an estimate of pain relief 90 minutes after administration of the materials to be tested. This pain relief which was judged by the patients' answer to the question, "Is your pain significantly less," was recorded as an "all or none" effect. Thus, the observer classified the result as either "analgesia" or "no analgesia." One of the advantages of this procedure was that it provided an experimental design which would permit the application of Chi Square analysis for statistical significance.

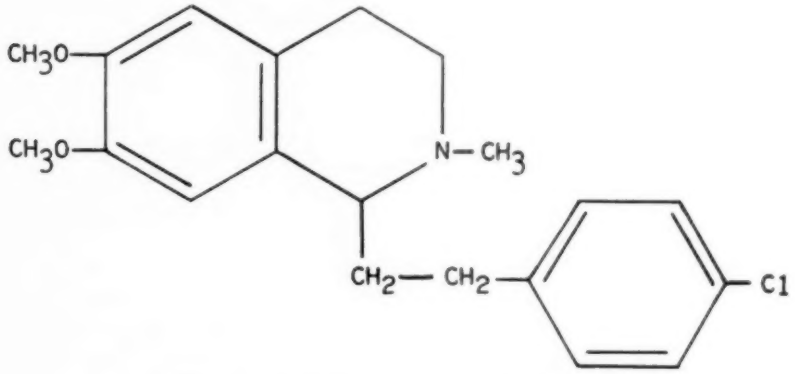

Fig. 1.—Structural formula of Ro 4-1778/1.

TABLE 1.—DISTRIBUTION OF DRUG ADMINISTRATION

Drugs Given to Each Patient	*No. of Patients*	*No. of Doses*						
			Dextropropoxyphene		*Codeine*		*Ro 4-1778/1*	
		Placebo	*32 mg.*	*65 mg.*	*30 mg.*	*60 mg.*	*30 mg.*	*60 mg.*
All	31	44	35	38	45	45	43	50
All but 60 mg. RO 4-1778/1	4	4	5	4	4	4	4	
All but 30 mg. codeine and 60 mg. Ro 4-1778/1	1	2	1	1		1	1	
Both doses propoxyphene and 30 mg. Ro 4-1778/1	1		3	1			1	
65 mg. propoxyphene, 30 mg. codeine, and 30 mg. Ro 4-1778/1	1			1	1		1	
Both doses dextro propoxyphene	5		6	5				
TOTALS	43	50	50	50	50	50	50	50

Fifty doses of each of the following materials were administered orally in a randomized fashion: placebo; codeine sulphate, 30 and 60 mg.; dextro propoxyphene hydrochloride, 32 and 65 mg.; and Ro 4-1778/1, 30 and 60 mg. Before the drugs were handed to the observer, each of the 350 doses was placed in an opaque, sealed envelope which was numbered according to its sequence in the randomization and stapled to the recording form. In this way, there was no opportunity for the observer or the patient to become aware of the code since every dose had a different number.

The distribution of drug administration among the 43 patients is shown in Table 1. We were fortunate from a statistical standpoint in that 31 patients received both doses of all 3 drugs and placebo medication at least once. Thus, 300 of the 350 doses were given to these 31 patients.

As collateral phases of the above controlled study, the following pilot trials were carried out. Single 60 mg. doses of Ro 1778/1 were given orally 2 to 6 times daily for periods of 6 weeks to 4 months to 10 patients who had chronic pain and did not tolerate codeine. Furthermore, Ro 4-1778/1 was administered intravenously to 15 patients (10 females and 5 males) in the recovery room, to relieve postoperative pain which we generally treat with 25 or 50 mg. meperidine.

Results. The analgesic effects in all 43 patients studied are shown in Table 2. It is apparent from visual inspection of these data that 60 mg. codeine and 60 mg. Ro 4-1778/1 were equally effective, as were the 30 mg. doses of these drugs.

Statistical analysis by Chi Square was made and the differences were considered significant if the "P" value was 0.05 or less. On this basis there was no significant difference between the effects of 65 mg. dextro propoxyphene, 60 mg. codeine and 60 mg. Ro 1778/1, on the one hand, and between 30 mg. codeine and 30 mg. Ro 4-1778/1 on the other. Thirty-two milligrams of dextro propoxyphene gave a response that was not significantly different from that of the placebo. The incidence of pain relief with 65 mg. dextro propoxyphene, 30 and 60 mg. codeine and 30 and 60 mg. Ro 4-1778/1 was significantly higher than with placebo. Codeine and dextro propoxyphene showed a dose-response relationship in that the larger doses of these drugs provided a significantly higher incidence of analgesia than the smaller doses. Obviously, the dose-response for dextro propoxyphene was to be anticipated since, statistically, the effect of 32 mg. was not significantly different from that of the placebo.

TABLE 2.—ANALGESIC RESPONSE: 350 DOSES IN 43 PATIENTS

Drug		*No. of Doses*	
		Analgesia	*No Analgesia*
Placebo		21	29
Dextro propoxyphene	32 mg.	27	23
Dextro propoxyphene	65 mg.	38	12
Codeine	30 mg.	33	17
Codeine	60 mg.	43	7
Ro 4-1778/1	30 mg.	35	15
Ro 4-1778/1	60 mg.	42	8

Since the findings presented in Table 2 might be criticized on the basis that not every patient received all of the materials studied, we analyzed the analgesic response in the 31 patients who received both doses of all three drugs and placebo medication. These data are summarized in Table 3. While these figures were different from those obtained in the analysis of pain relief

in all patients, the statistical significance of the drug responses remained unchanged. These statistically significant differences ($P<0.05$) were as follows:

All drugs except 32 mg. dextro propoxyphene versus placebo

65 mg. dextro propoxyphene versus 32 mg. dextro propoxyphene

60 mg. codeine versus 30 mg. codeine

60 mg. codeine versus 32 mg. dextro propoxyphene

30 mg. Ro 4-1778/1 versus 32 mg. dextro propoxyphene

60 mg. Ro 4-1778/1 versus 32 dextro propoxyphene

60 mg. Ro 4-1778/1 versus 30 mg. codeine

These results may be interpreted to indicate that, under the conditions of this study, all of the drugs except 32 mg. dextro propoxyphene were more effective than placebo medication; that the larger doses of all three analgesics produced analgesia more frequently than 32 mg. dextro propoxyphene; that 60 mg. of both codeine and Ro 4-1778/1 were more effective than 30 mg. codeine and that the incidence of pain relief with 30 mg. Ro 4-1778/1 was higher than with 32 mg. dextro propoxyphene.

That a dose-response relationship was obtained with codeine and dextro propoxyphene indicates in some measure the validity of the clinical design.

Statistically, there was no significant difference between the effects of the higher dose levels of the three analgesics. Thirty milligrams of codeine produced analgesia not significantly more often than 32 mg. dextro propoxyphene. Thirty milligrams of Ro 4-1778/1 was not significantly more effective than 30 mg. codeine.

The higher dose levels of all three drugs produced analgesia not significantly more often than 30 mg. Ro 4-1778/1. Finally, 65 mg. dextro propoxyphene was not significantly more effective than 30 mg. codeine.

TABLE 3.—ANALGESIC RESPONSE OF 31 PATIENTS RECEIVING DOSES OF ALL DRUGS

Drugs		*No. of Doses*	
		Analgesia	*No Analgesia*
Placebo		16	28
Dextro propoxyphene	32 mg.	15	20
Dextro propoxyphene	65 mg.	27	11
Codeine	30 mg.	28	17
Codeine	60 mg.	38	7
Ro 4-1778/1	30 mg.	31	12
Ro 4-1778/1	60 mg.	42	8

As in our earlier study[3], we observed but one untoward reaction and this was in a patient who developed headache after the administration of codeine. This low incidence of untoward reactions may be due, in part, to the fact that none of the patients was ambulatory.

Good results were obtained in the 10 patients who received Ro 4-1778/1 for prolonged periods. Three representative case histories follow:

A woman, in her seventh decade, had severe "burning" pain along the lines of incision following radical mastectomy. She could not tolerate codeine because it consistently produced

nausea, vomiting and diarrhea. The administration of dextro propoxyphene and ethoheptazine in combination with aspirin were without significant beneficial effects. She had a very low tolerance for narcotics such as meperidine. Sixty milligrams of Ro 4-1778/1 were given orally 2 to 6 times daily for 4 months. The burning sensation was relieved for several hours. There were no disturbing side effects.

A woman, in her sixth decade, had chronic severe pain of biliary colic. We were reluctant to use narcotics because of the nature of her pain and her relatively unstable basic personality. She was given 60 mg. Ro 4-1778/1 orally 3 to 4 times daily for 6 weeks. Pain relief after each dose lasted for about 2 hours. There were no side effects and her only complaint was that in some instances it took as long as 40 minutes before pain relief became significant.

The third patient was a woman in her fifth decade who had a severe capsulitis. She could not tolerate oral doses of 30 mg. codeine because of nausea, giddiness and constipation. She was given 60 mg. Ro 4-1778/1 orally q.i.d. for 7 weeks with good relief of pain and without any side effects.

A summary of our findings in the 15 cases which were given Ro 4-1778/1 intravenously follows:
The first 2 patients received single doses of 10 mg. Ro 4-1778/1. There was no apparent effect. The next 2 patients were given single doses of 20 mg. One fell asleep in about 45 minutes and in the other there seemed to be some pain reduction. The remaining 11 patients received single doses of 30 or 40 mg. The total doses given within 2 hours were 70 mg. in 2 cases and 80 mg. in one instance. Nine of these 11 patients had some analgesic response. Duration of analgesia was 45 to 60 minutes. One patient complained of nausea 90 minutes after the injection. There was no evidence of central, respiratory, or circulatory depression. We are continuing to expand our experience in the recovery room in order to determine the most effective dose and route of administration.

Discussion. Evaluation of a new analgesic agent at an early stage of its development is difficult. Controlled double blind procedures can be employed in an attempt to gain unprejudiced data. Yet, the value of a study such as that presented is limited because it is concerned with one type of pain only. Further work is required to demonstrate the effectiveness of Ro 4-1778/1 in pain situations other than skeletal-muscular pain. On the basis of our present work there can be hardly any doubt that in orthopedic pain Ro 4-1778/1 is as effective as codeine or dextro propoxyphene. In fact, the incidence of pain relief with 30 mg. Ro 4-1778/1, but not with 30 mg. codeine, was significantly higher than with 32 mg. dextro propoxyphene. Moreover, both 65 mg. dextro propoxyphene and 60 mg. codeine produced analgesia not significantly more often than 30 mg. Ro 4-1778/1. While we cannot make any definitive statements regarding the relative incidence of side reactions to codeine and Ro 4-1778/1, our limited experience in patients with chronic pain suggests that the drug may be useful in cases which are unable to tolerate codeine.

Change in mood, euphoria, and the development of tolerance have not been observed. Since some patients were given Ro 4-1778/1 for several months followed by abrupt discontinuance without the appearance of abstinence signs, it is anticipated that the drug has no or very low addiction liability.

This expectation is supported by the results of the studies in monkeys by Deneau and Seevers[2]. These investigators estimated the physical depen-

dence capacity of Ro 4-1778/1 to be "very low."

Experience with the intravenous administration of Ro 4-1778/1 in doses of the same order as those which were used orally, suggests that the drug has a good margin of safety. The absence of central, respiratory, and circulatory depression is encouraging.

Summary. 1. A double blind, controlled study of analgesic drugs was made in 43 male patients on the surgical orthopedic wards. Fifty oral doses each of the following were administered: Thirty-two and 65 mg. dextro propoxyphene hydrochloride, 30 and 60 mg. codeine sulphate, 30 and 60 mg. of an experimental analgesic, Ro 4-1778/1, and a placebo.

2. All analgesics except 32 mg. dextro propoxyphene were significantly more effective than the placebo.

3. Sixty-five milligrams of dextro propoxyphene, 60 mg. codeine, and 60 mg. Ro 4-1778/1, provided similar analgesic effects.

4. Ten patients with chronic pain, who could not tolerate codeine, were given 60 mg. doses of Ro 4-1778/1 orally 2 to 6 times daily for 6 weeks to 4 months, with beneficial effects.

5. Ro 4-1778/1 was given intravenously in doses of 10 to 40 mg. to 15 postoperative patients in the recovery room. Pain was obtunded for 45 to 60 minutes after doses of 30 to 40 mg. There was no evidence of central, respiratory, or circulatory depression.

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SUMMARIO IN INTERLINGUA

Un Studio a Controlo, de Codeina, Dextro-Propoxyphen, e RO 4-1778/1

1. Un bis-occulte studio a controlo esseva facite de drogas analgesic in 43 patientes mascule del section chirurgico-orthopedic. Cinquanta doses oral de cata un del sequentes esseva administrate: 32 e 65 mg de hydrochloruro dextro-propoxyphenic, 30 e 60 mg de sulfato de codeina, 30 e 60 mg de un analgesico experimental designate como Ro 4-1778/1, e un placebo.

2. Omne le analgesicos, con le exception de 32 mg de dextro-propoxyphen, esseva significativemente plus efficace que le placebo.

3. Sexanta-cinque milligrammas de dextro-propoxyphen, 60 mg de codeina, e 60 mg de Ro 4-1778/1 provideva simile effectos analgesic.

4. Dece patientes con dolores chronic qui non poteva prender codeina recipeva doses oral de 60 mg de Ro 4-1778/1 inter 2 e 6 vices per die durante periodos de inter 6 septimanas e 4 menses, con effectos benefic.

5. Ro 4-1778/1 esseva administrate per via intravenose in doses de inter 10 e 40 mg a 15 patientes post-chirurgic in le sala de restablimento. Le dolores esseva obtundite pro inter 45 e 60 minutas post doses de inter 30 e 40 mg. Esseva notate nulle signo de un depression central, respiratori, o circulatori.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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THE HYPERSENSITIVE STATE AND THE LIVER: A CRITICAL REVIEW

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THERE is increasing awareness of possible immunologic mechanisms in obscure liver disease. Of interest recently has been the observation of granulomatous lesions in the livers of patients with chronic ulcerative colitis, rheumatic fever, rheumatoid arthritis, and in association with involvement of other organs by immunologic processes. Drugs have been implicated in hepatic disease through a process of sensitization. These observations have stimulated interest in the responsiveness of the liver to antigenic stimulation. Does the liver participate in allergic phenomena occurring elsewhere in the organism; and what are the hepatic lesions produced by an antigenic stimulus? The literature pertaining to these questions is critically reviewed as a basis for future studies.

THE PATHO-PHYSIOLOGY OF THE LIVER IN ANAPHYLACTIC SHOCK. Manwaring[90-93] observed that shunting of the blood from the portal vein to the caval system prevented anaphylactic shock in sensitized dogs. Re-establishment of the normal circulatory relationships restored the response, with severe shock after eliciting intravenous re-injections of antigen. Perfusion of a lung preparation from sensitized guinea pigs with

specific antigen caused spasmodic contraction of bronchioles and pulmonary blood vessels, as evidenced by the reduced rate of outflow. If the specific antigen was administered with blood from an anaphylactic animal there was no change in the rate of flow in the lung preparation. Manwaring concluded that vasodilatory substances were released from the liver of the anaphylactic animal and caused shock, while antithrombic substances prevented coagulation of the blood. Denecke[30] confirmed these observations in dogs with the classical Eck fistula. When these animals were sensitized and challenged 3 weeks later with the specific antigen, anaphylactic shock did not ensue. Normal dogs developed violent reactions.

Mautner and Pick[96] studied the rate of flow from the hepatic vein of the surviving liver. Normally, there is a steady and uniform deflux time. After perfusion with histamine or peptone there is first an increased rate of flow and then a significant decrease or cessation of flow. The livers of dogs sensitized with horse serum reacted similarly when horse serum was added to the perfusion fluid. Peptone, histamine and anaphylactic shock caused closure of the hepatic veins, while the inflow through the portal vein was unchanged. Closure of the hepatic veins has been considered by the authors fundamental to the occurrence of anaphylactic shock.

These studies were confirmed later by Weil[136], who also studied preparations of surviving liver from sensitized dogs. When the liver was perfused with blood containing the antigen, the blood from the hepatic vein was incoagulable. Symptoms of shock could be traced to the effect of the specific antigen on the sensitized liver.

More recently, Maegraith *et al.*[88], in experiments with dogs, rats, guinea pigs and rabbits, injected specific antigen locally beneath the capsule of the liver after previous laparotomy in sensitized animals. The injected area was congested and a similar congestion of an entire lobe occurred when the antigen was injected into the portal stream. Constriction of the hepatic vein with severe centri-lobular congestion and necroses developed in the parenchyma of the liver. Through reversal of the Eck fistula, by ligating the inferior vena cava, anaphylactic shock was produced in the sensitized animals. However, vasodilators and antithrombic substances never were demonstrated.

Bauer[9] found, during anaphylactic shock in dogs, contraction of sphincteric mechanisms at the caval ostia of the hepatic veins. This sluice mechanism, sensitive to histamine, was evident in dogs, absent in cats and inconstant in the goat.

Chanin[19] produced anaphylactic shock in dogs with intravenous injections of heterologous blood; he noted spasm of hepatic veins, absent in dogs with Eck fistula; and concluded that the liver plays an important role in the symptomatology of shock in sensitized dogs. Of interest is the observation of Friedberger and Seeling[44] that extirpation of the frog liver renders frog serum non-toxic for rabbit erythrocytes.

The liver clearly plays an important role in the occurrence of anaphylactic shock and exclusion of the liver from the circulation may prevent such an event. The basic principle of the anaphylactic shock is an antigen-antibody interaction; consequently, the pathophysiological experiments cited have a direct bearing on this subject.

EXPERIMENTAL HYPERSENSITIVE STATE IN THE LIVER. Delezenne[29] repeatedly injected emulsions of dog liver intraperitoneally into rabbits. The rabbit serum was exceedingly toxic when injected into dogs. Some died immedi-

ately; other dogs developed glycosuria and died. At necropsy, the livers were yellow and friable. Microscopically, there was fatty degeneration of liver cells, vascular engorgement, lymphatic dilation and round cell infiltration. This effect was organ-specific; these phenomena were not observed in other organs or in controls.

Bierry and Mayer[12] and Bierry and Pettit[13] reported in 1904 their experiments with "nucleoprotéides" of dog liver repeatedly injected into rabbits. After injection of such rabbit serum into dogs, congestion, fatty, vacuolar and granular degeneration of the liver were observed. Since "nucleoprotéides" of dog kidney give rise in similar conditions to albuminuria and histologic changes in the kidneys, the authors concluded that serum obtained with nucleoprotéides has cytotoxic properties for the organ source of the nucleoprotéides.

Pearce[114] observed lesions in the livers of animals receiving intravenous injections of sera from animals sensitized with the red cells of the former. Areas of necrosis were observed; the capillaries contained masses of coalesced red blood cells, seen also in smaller veins. The author assumed that this phenomenon was peculiar to the liver because of the slow blood flow in the portal system.

Karsner and Aub[74] described changes in livers of sensitized cats when immune serum was used for perfusion of the liver; hyaline necroses were observed, which were absent in controls.

Joannovics[73] injected minced cat liver intraperitoneally into rabbits for a prolonged period of time. The rabbit serum, injected into 6 cats, caused immediate death in 2 animals. Three animals died 1, 2 and 4 months after the injection of cachexia. There was fatty metamorphosis of hepatic cells and disappearance of entire liver lobules, replaced by proliferation of cellular connective tissue. Other organs were normal.

Alessio[2] injected horse serum into the livers of sensitized rabbits. At necropsy, there were plasma cells between trabeculae and reticular cells around bile canaliculi. No thromboses or hemorrhages were observed. The changes resembled those previously obtained by the author in the stomach.

Croizat[26,27] made a detailed study of the histologic changes in liver cells in guinea pigs and rabbits sensitized to egg-albumin. There were phenomena of lysis of the "chondriome." Hepatic lesions were not as impressive as those in the lungs; but fatty changes and vacuolar degeneration of hepatic cells developed frequently following repeated eliciting injections.

Choi[21] injected horse serum directly into the liver in rabbits sensitized 3 weeks earlier to the same substance. The histologic changes included hemorrhage, pronounced eosinophilic infiltration and intense inflammatory exudate. The unsensitized controls receiving the same injections into the liver did not present such changes.

Masugi[95], known for his work with nephrotoxic sera, used rats for the study of hepatotoxic sera. Their action appeared first in capillaries in the lobular periphery, consisting of collections of leukocytes and endothelial proliferation. With higher doses, necroses of hepatic cells appeared, and fibrinous thrombi and hemorrhage, as noted in eclamptic states.

Apitz[3] made a detailed study of the histopathology of acute anaphylactic shock and of changes occurring in the liver in protracted cases. In the latter, the changes observed in the liver were: centroacinar necroses, fatty degeneration in the liver cells around necrotic areas, cellular infiltrates near the cen-

tral veins; portal areas were wide and contained histiocytic infiltrates; and giant cells, some resembling large histiocytes.

Kishioka[77] injected solutions of dried rabbit liver into rabbits and so produced iso-antibodies after multiple injections. Antigenicity of liver tissue has been induced by mechanical damage, by warming or freezing of liver. The presence of antibodies was detected by the precipitin reaction method and by complement fixation tests.

Martin and Croizat[94] returned to the problem of fine cellular details of the hepatic cells after anaphylactic shock, acute or chronic. Remarkably, there were no inflammatory changes in the guinea pigs examined 8 to 14 days after the challenging injection. Changes in the liver may involve parenchymatous elements rather than mesenchymal structures.

Hartley and Lushbaugh[59] injected crystalline egg-albumin (3% into the radicles of the mesenteric veins, into the marginal vein of the ear, the spleen and into the abdominal cavity of sensitized rabbits. Necrotic lesions developed in the liver of those animals receiving the challenging injection into the mesenteric veins. Other routes of challenging injection yielded similar findings. The authors assumed that hepatic cell necroses may occur as a consequence of antigen-antibody union.

Estes[37] injected rabbit anti-rat liver serum into rats in small amounts over a prolonged period, and larger amounts over short periods of time. With rat liver injected into rabbits, precipitins appeared, specific for rat liver. The group of rats receiving injections every other day for periods up to 2 weeks demonstrated necrosis of hepatic cells, mononuclear infiltration, with lymphocytes, eosinophils and granulomas with giant cells. Other organs were normal.

Meyer-Krahmer[99] studied the action of hepatotoxic serum in dogs and rats. Changes in 14 of 17 dogs consisted mostly of swelling of liver cells with vacuolar degeneration, but without fatty changes. In 3 animals, changes were more severe, with trabecular dissociation, dilation of the spaces of Dissé and exudate filling the capillaries. Findings had returned to normal in 6- to 14-week specimens. Similar changes in the liver were observed when myotoxic sera, obtained by injection of muscle tissue, were injected into animals. Rats, injected with serum obtained according to Masugi's procedure, developed hepatic lesions. The relative specificity of anti-organ sera was emphasized.

Vorlaender[132] injected saline suspensions of rabbit liver into rabbits, using as adjuvants dead bacilli of bovine tuberculosis. Antibody formation was evident from the positive complement fixation tests. These antibodies were organ specific and reacted again when incubation with bacilli of bovine tuberculosis eliminated the corresponding antibody. Frick[43] used the same method, with similar results.

Maekawa[89] tried to purify the fraction responsible for tissue sensitization and concluded, after many years of study, that a phosphatide fraction functions as a hapten in such sensitization. Such phosphatides from red cells in conjunction with ox serum caused severe anemia of the acquired type. Scheiffarth[116] tried to duplicate Maekawa's results using a phosphatide, extracted from albino rat livers; however, experiments performed with adequate controls failed to disclose any specificity to such liver phosphatides.

Alessio[2] and Choi[21] produced an Arthus type of response in the liver. The localized Schwartzman reaction was studied by Apitz[4], by Gerber[50] and by Alechinsky[1], attention being directed to changes occurring in the

liver, while the preparatory site was different than the liver. Apitz[4] described focal necroses after the eliciting injection; Gerber[50] observed foci of necrosis and venous thrombi in the central veins after a single injection of filtrate of Gram-negative bacteria. These thrombi were composed of masses of eosinophils, erythrocytes and polymorphonuclear cells. Subendothelial infiltrates also were present. Alechinsky[1] confirmed the observations of Gerber. Twenty-four hours after the preparatory injection, there were focal necroses in the vicinity of the central vein. The hepatic veins were dilated and filled with eosinophils. These lesions were more severe after the challenging injection. Fibrinous thrombi in the subhepatic veins were numerous. Black-Schaffer *et al.*[14] produced the Schwartzman phenomenon with filtrates of purpurigenic and non-purpurigenic meningococci. In both cases, focal necroses of the liver was observed.

In summary: two methods have been employed to study the reactivity of the liver to the challenge of a specific antigen. The first method consists of injection of hepatotoxic sera. Lesions consist of parenchymal-cell-degeneration, focal necroses and replacement of liver tissue by connective tissue elements. The second method consists of local injection into the substance of the liver of a specific antigen to which the animal has been previously sensitized. Reactions are not unlike those produced by a similar mechanism in other organs. The antigenicity of liver tissue has been investigated by several authors using the precipitin and the complement fixation reaction. There is experimental evidence that the liver is responsive to antigenic stimulation, reacting with degenerative phenomena of the parenchymal elements and with proliferative phenomena of the mesenchymal elements.

HYPERSENSITIVITY IN CLINICAL LIVER DISEASE. Hypersensitivity apparently can involve the liver of man also. Messen and Merkel[97] described a fatality after repeated injections of TAB vaccine in a 52-year-old man. Necropsy demonstrated cellular foci in lobular peripheries and in portal spaces, composed of histiocytes and granulocytes. The authors tried to reproduce these clinical and pathological changes in animals, using similar and identical vaccines. They were successful in reproducing the histopathological changes in the livers in 45 of 63 white rats injected with TAB vaccine and in 6 of 13 treated repeatedly with the Breslau vaccine. Some animals died from the procedure. Sumner[126] described a girl who died after the intramuscular injection of 2.5 ml. of horse serum with diphtheria antitoxin. The patient often had developed conjunctival irritation and a nasal discharge when near horses. The clinical picture was that of anaphylactic death. At necropsy, severe hepatic lesions included vascular engorgement with leukocytes, hemorrhage and liver cell necrosis. Dean[28] described a soldier who died after repeated injections of antitetanus serum. The liver grossly was purplish red in color and contained excessive blood. Liver sinusoids were engorged and filled with leukocytes. The liver cells had an empty, vacuolated appearance. There were many eosinophils. The connective tissue around branches of the portal vein and bile ducts were filled with leukocytes. Siegmund[121] described a 20-year-old soldier who died after an intravenous injection of tetanus antiserum after having received previous injections of the same drug. The liver had disorganized trabeculae; Kupffer cells were increased in size, rounded and detached. Capillaries contained very many leukocytes. Flandin[39] observed

jaundice in a young patient following repeated injections of horse serum. The concurrent symptoms of urticaria, pruritus, general sweating, and a local Arthus reaction of the skin testified, according to the author, to the hypersensitive nature of the disease. Oudard and Jean[112] described a case of a 21-year-old man who, at the reinjection of horse serum, experienced fatigue, nausea, urticaria, followed by enlargement of the liver with jaundice. The author considered these hepatic signs and symptoms expressions of a serum sickness. Flandin and Vallery-Radot[40] described the symptoms of urticaria and fever in a man who received repeated injections of serum. Five days later, there was jaundice and increase in size of the liver. The skin test with the same serum later was negative; interpreted by the authors, as desensitization caused by the anaphylactic condition. In the above mentioned cases the evidence of a hypersensitivity basis for hepatic symptoms is indirect, but suggestive. The literature contains many observations in which hypersensitivity has been assumed on a much less convincing basis. For the sake of completeness, several such reports are reviewed. Bronchial asthma is one of the conditions in which the liver has been observed to participate in the clinical symptoms. Some authors thought the liver disease predisposes to asthma; others thought that the manifestations of hepatic origin are part of the hypersensitivity reaction of which liver symptoms and asthma are part. Gilbert and Villaret[51] were impressed with the increase in size and tenderness of the liver in asthmatic patients, at a stage in which cardiac insufficiency presumably could not play a role. Mussio-Fournier and Sloane[106], mindful of the alleged inter-relation of asthma and hepatic symptoms, described an interesting case in which hydatid disease of the liver apparently was the cause of asthma, Quincke's edema and urticaria. Moncorgé[102] studied 315 asthmatic patients, in most of whom liver tenderness was elicited; others had had in their past, jaundice, colic, migraine and urticaria. This work without controls fails to clarify this problem. Turiaf and Blanchon[128] returned recently to the same subject and described cases with asthma, pulmonary infiltrates and painful enlargement of the liver. Their conclusion, based on clinical speculation only, was that the lesion of the liver and the pathologic state of the bronchi are expressions of the same antigen-antibody relationship. No objective evidence has been produced for this assumption. Hemolytic anemia associated with cirrhosis of the liver has intrigued many clinicians. Hyman and Southworth[72] collected 21 such cases and speculated that a "metabolite" secondary to hepatic injury acting as an antigen could produce abnormal antibodies and cause red cell-destruction. However, no scientific investigation of this problem has been undertaken with modern techniques.

There is no doubt that the liver has participated in the pathology of those cases in which death resulted from use of antisera or vaccines[28,97,121,126]. In such instances hepatic changes were similar to those seen in the experimental animal. In other cases, lacking corroboration by tissue diagnosis, the possible role of the liver in phenomena of hypersensitivity was only presumptive. Some symptoms considered by the authors indicative of a hypersensitive state are nonspecific and controversial, including erythema, arthralgia, migraine, and others. Most of the clinical observations on hypersensitivity reactions of the liver lack objective scientific evidence. Such information is difficult to obtain and the hypersensitive nature

of hepatic disease, therefore, has been accepted in the past with the utmost reluctance.

HYPERSENSITIVITY AND INFECTIOUS HEPATITIS. Some cases of infectious hepatitis are accompanied by symptoms of apparent allergy, such as urticaria, erythema and arthralgia. These phenomena may occur in homologous serum jaundice and viral hepatitis type A. Mirick[101] reported allergic manifestations in 54.8% of 300 patients of the Cleveland epidemic, including hives, angioneurotic edema, purpuric rashes and arthralgias. Hawley *et al.*[64] found headaches in 25%, arthralgias in 25% and urticaria and rashes in 40% of cases of jaundice after injection of convalescent mumps serum. Other authors[18,131] reported similar observations. Mutzner[107] theorizes, without evidence, that the jaundice of infectious hepatitis is a manifestation of liver hypersensitivity. Several authors[32,45,81] include the allergic manifestations in a subgroup of the clinical picture of acute hepatitis. Frugoni and Coppo[45] include in this group certain instances of jaundice in which the pathogenesis can be explained by the interaction of an allergen with its antibody, as in the jaundice in serum sickness, in erythema nodosum and in anaphylactic shock. Such cases are characterized by inflammatory changes in the mesenchymal tissues. Here fits well, according to these authors, the concept of serous hepatitis described by Eppinger *et al.*[36]. However, these speculations are based on unspecific symptoms and lack scientific validity. Some authors consider allergic sensitization a factor in severe infectious hepatitis leading to acute yellow atrophy and death. The virus of infectious hepatitis has not been isolated as yet by inoculation in a laboratory animal or in tissue culture. An immunological test of its diagnosis, therefore, was necessary. Hemagglutination tests with *Macacus rhesus* erythrocytes[105] and, particularly, with chick cells[62] have yielded promising results, but as Havens[63] states, these tests support and suggest immunological phenomena accompanying viral hepatitis, but provide no absolute evidence. The same author[61] had used the collodion particle agglutination test, with positive results in a high percentage of acute phase sera of infectious hepatitis; but a high proportion of positive results have been obtained in acute febrile diseases. The lack of a specific diagnostic test for infectious hepatitis has hindered the understanding of the possible immunology of this disease. The antigenic properties of the virus will be studied and understood only after the virus is isolated. Cohen *et al.*[23] have used fluorescein-stained anti-human gamma globulin serum and observed large amounts of gamma globulin in the liver in acute hepatitis. This finding is significant, since gamma globulin is absent in the normal liver.

In summary, the past impression of hypersensitivity playing a role in infectious hepatitis was based on clinical association with nonspecific symptoms. Immunological tests have been attempted in the past mostly for diagnostic purposes; the most they offer is a hint that hypersensitivity may participate in some part of the disease process. The identification of large amounts of gamma globulin in the liver in infectious hepatitis by Cohen *et al.*[23] is an important first step and should be confirmed by more extensive studies.

HYPERSENSITIVITY AND DRUG-INDUCED LIVER DISEASE. It has long been suspected[48] that jaundice appearing in the course of arsenical therapy may have a hypersensitive origin. Cutaneous rashes and passive sensitization of guinea pigs were strongly suggestive of such a mechanism. So were toxic phenomena for doses normally well

tolerated and for severe reactions accompanied by shock. Tzanck *et al.*[129] collected a large series of syphilitic patients treated with arsenicals in whom jaundice occurred. Twenty-five percent had accompanying symptoms of rash or urticaria, nitritoid crisis and arthralgia. The number of cases with symptoms of intolerance was large[24] and had been a problem in antiluetic therapy. It is of interest that Miles[100] observed positive complement fixation reactions in the sera of patients with postarsphenamine jaundice. Hanger and Gutman[58] made a thorough study of 12 cases of postarsphenamine jaundice and defined their histopathological features as those of a cholangiolitis and pericholangiolitis. They suggested a hypersensitivity mechanism because of the onset after the second or third injection, the induction of jaundice by very small amounts of the drug and by the presence of rashes, arthralgias, edema and eosinophilia.

Hypersensitivity may be frequent with sulfonamide therapy[42,66]. Multiple courses of treatment are particularly important in promoting allergic reactions. The liver has been found involved in such cases, with infiltration of histiocytes, focal necroses and microabscess formation. In toxic necrosis of the liver caused by cinchophen[113], skin reactions were interpreted as due to a hypersensitivity factor. The list of drugs potentially dangerous to the liver is extensive. In recent years chlorpromazine[125] has gained therapeutic prominence. Hepatitis induced by this drug may be mild and fleeting or may be prolonged[125], even after a single tablet. It may occur after the drug had been discontinued[11,98] for 2 or more weeks. Patients with previous hepatic function abnormalities seem to be more prone[7] to chlorpromazine damage.

Elliot *et al.*[35] observed beneficial therapeutic results in chlorpromazine jaundice from cortisone. They vaguely mentioned the possibility of a hypersensitivity mechanism. Arias and Zamcheck[5] found a decreasing concentration of bromsulphalein in the duodenal drainage after injection of chlorpromazine and postulated an interference with dye excretion, suggesting the possibility of a mechanism unrelated to hypersensitivity. These observations should be confirmed. By far, the most popular concept of the mechanism of chlorpromazine jaundice is that of an allergic mechanism. Hollister[69] particularly has advocated an allergic mechanism because of the time and onset of symptoms, eosinophilia of the portal areas, eosinophilia of the peripheral blood and because of prompt recurrence after challenge with the drug. Shay and Siplet[118] studied various compounds of the promazine structure and demonstrated that the drug hypersensitivity is related to molecular structure and that desensitization may occur through continuous therapy or through repeated reactions. Zelman[140] recently pointed out the consistent findings of liver cell necrosis in chlorpromazine jaundice, in addition to cellular infiltrates in the periportal areas. He considers the allergic mechanism as "adequately" presented by Hollister[69]. It is of interest that prochlorperazine, found inactive in chlorpromazine jaundice by Shay and Siplet[118], recently has been[123] reported as the cause of jaundice. However, the literature contains only suggestive evidence of a hypersensitivity mechanism in drug jaundice; direct immunologic methods are needed to elicit the incontrovertible evidence of an antigen-antibody relationship.

The clinical criteria of drug hypersensitivity included in the past a clinical history of allergy, the fact that the drug has been well tolerated on previous occasions, symptoms provoked by small amounts of the drug, a latent

period of 5 to 9 days and a symptomatology suggestive of phenomena of hypersensitivity, including urticaria, arthralgia, fever and asthma. These criteria seem insufficient and direct evidence is required of drug-induced liver disease. The link between the drug and the observed liver lesion could be based on a variety of immunologic procedures. The indirect evidence could be obtained through the precipitin test with a test antigen after the drug has been coupled to the patient's serum proteins and antibodies obtained after injection into rabbits. Such drug sensitivity may be transferred passively through serum or through cells. The inhibition of a Schultz-Dale phenomenon by the drug also has the value of proof that a drug can serve as a hapten and cause sensitization. The direct evidence is obtained when the drug-protein complex is found bound to liver tissue in the liver substance. Such direct evidence is obtainable with tagged material, as will be pointed out in the discussion.

CHRONIC LIVER DISEASE OF POSSIBLE IMMUNOLOGICAL ORIGIN. A strikingly homogenous clinical syndrome has become apparent in the last decade. Waldenström[133] first described 6 cases of severe liver disease in young women, characterized by a large, firm liver, jaundice, spider nevi and increased amount of gamma globulin in the blood serum. The erythrocyte sedimentation rate was high and there was a highly positive formol-gel test. These patients responded well to corticotropin. The gamma globulin-peak on paper electrophoresis resembled that of liver cirrhosis in that it was broad based. Bearn *et al.*[10] reported a large group of young women with progressive liver disease, characterized by painless jaundice, febrile episodes and joint pains. The liver and spleen were considerably enlarged, while acne, hirsutism, obesity and moon face suggested a concomitant endocrine disturbance. The gamma globulin levels of the blood serum were increased to 9.4 gm.%. Liver biopsies or necropsy findings indicated diffuse nodular cirrhosis with severe infiltration of chronic inflammatory cells. The assumption that the above cases had a hypersensitivity mechanism is based only on indirect clinical evidence. Mackay *et al.*[87] called attention to a similar group of patients: mostly young women with severe liver disease and a positive LE phenomenon. Half of the patients had an insidious onset; others started as in acute hepatitis. Half of these patients had joint pains, some had skin rashes. A few patients developed chronic renal disease, 3 of them had concomitantly chronic ulcerative colitis. All responded well to cortisone therapy. The authors considered the disease a manifestation of hypersensitivity reaction in the liver and the LE phenomenon an indication of the presence of antibodies against leukocytes. LE cells have been found by others in chronic liver disease without necessarily signifying co-existing disseminated lupus erythematosus[8,55,76,120,124,130]. Conversely, the group described by Bartholomew *et al.*[8] had severe manifestations of systemic lupus erythematosus and severe liver disease. If one accepts the pathogenesis of systemic lupus erythematosus as a manifestation of sensitization to DNA-protein[6], liver disease in these cases may be the result of such sensitization. Here again, the paper of Bartholomew *et al.*[8] deals with clinical material and no direct evidence of a hypersensitivity mechanism has been presented.

AUTOIMMUNITY AND THE LIVER. The recent literature contains accounts of autoantibody-conditioned diseases, and the concept of autoimmune disease has become fashionable. How do objective facts justify such a concept? The

first break in the theory of "horror autotoxicus" of Ehrlich[58] based on observations made by Ehrlich and Morgenroth[34] came shortly after it had been first formulated. Widal *et al.*[138] and Chauffard[20] demonstrated that a patient's serum in cases of acquired hemolytic anemia may lyse his own red blood cells. These antibodies, however, had the character of iso-antibodies, and auto-antibodies have probably yet to be proven to be the mechanism of acquired hemolytic anemia. The auto-immune disease concept has been applied frequently to chronic thyroiditis. Witebsky *et al.*[139] made observations which seem to fulfill all requirements of an autoimmune disease mechanism. There has been a demonstration of free antibody; the antigen has been identified as thyroglobulin. The disease has been reproduced in the experimental animal, and the histopathological findings were similar to those of the naturally occurring disease. Gear[49] has been an advocate of an auto-immune mechanism in liver disease. Hughes[70] observed that in homologous serum jaundice, following yellow fever vaccination, the serum of patients in the acute phase of the disease reacted with that of the convalescent phase causing a positive precipitin reaction. Similarly, serum of convalescent patients reacted with human liver extracts. Gear[49] assumed that yellow fever virus renders the liver antigenic and capable of provoking an antibody response. The auto-immune liver damage may persist, again by speculation, long after the original damaging influence had ceased to act.

Eaton *et al.*[33] described a heterogenetic antibody in certain cases of acute infectious hepatitis which agglutinated red cells of sheep, rabbits, horses, rhesus monkeys and cows. This heterophile antibody could be absorbed by human liver tissue in the complement fixation test.

An auto-immune mechanism for liver disease also has been claimed by Gajdusek[46,47,83]. He matched sera of patients with different diseases with saline suspensions of homogenized tissues, particularly liver, and obtained specific complement fixation reactions in disseminated lupus erythematosus, in "lupoid" hepatitis and in macroglobulinemia. In the first two diseases the complement fixation test was positive in 75% of cases, mostly at a titer above 1:16. Human liver tissue injected into rabbits, guinea pigs and rats provoked a high titer complement fixation response. However, even in cases with high complement fixation titer, the serum of the patients failed to react with their own organs[86]. A basic requirement for the auto-immune theory, therefore, is lacking. Mackay and Larkin[84] were aware of the lack of organ specificity in complement fixing "auto-antibodies" and, of the lack of reactivity when tested with the patient's own tissues. In a more recent study[85] sera from 7 patients with high titers for iso-immune tissue antigens failed to react with antigens from their own tissues. However, 6 other patients had positive reactions. Further investigation of this subject on larger numbers of patients seems necessary. Vorlaender[132] was able to reproduce the complement fixation reactions when saline suspensions of liver tissue of rabbits were tested against serum of the rabbits sensitized with such suspensions. Dead bovine tuberculosis bacilli were used as adjuvants. Positive reactions were obtained when sera of patients with infectious hepatitis were tested against extracts of acute yellow atrophy liver. These phenomena, absent in controls, are, therefore, valid and denote that immunologic changes occur during the course of liver disease. However, the observations should not be regarded as new, since the flocculation test of Kahn, in use for many

years, is based on a similar mechanism. The significance of tissue antibodies in the pathogenesis of human disease decreases, when one realizes that they appear after the onset of disease and they decrease after recovery. They may maintain a tissue reaction after the disease has been initiated when the etiologic factors have ceased to act; their presence may serve as indication of continued clinical activity.

LIVER CIRRHOSIS AND THE HYPERSENSITIVE STATE. Since cirrhosis of the liver usually is an end result of different pathologic processes, it would seem difficult, *a priori*, to trace its genesis to immunologic phenomena. There are a few reports of experimental cirrhosis produced in animals. Wells[137] produced liver cirrhosis in 4 rabbits after repeated intravenous injection of peptone. Longcope[80] injected horse serum or egg white subcutaneously in sensitized guinea pigs, rabbits, cats, and dogs. Rabbits inoculated over prolonged periods of time developed dense connective tissue and the fine nodularity of true liver cirrhosis. While most of the rabbits developed hepatic lesions and 4 of 9 cats had similar changes, none of the dogs or guinea pigs presented such a response. It had been noticed long ago that babies dying from erythroblastosis fetalis may have hepatic lesions consisting of necroses, fibrosis or cirrhosis. Craig[25] had observed such cases and considered Rh incompatibility as a possible cause of cirrhosis of the liver. Myers *et al.*[108] reported a case of apparent chlorpromazine jaundice in a 31-year-old man who, 5 months later, underwent an exploratory laparotomy because of the uncertain diagnosis. The histologic appearance of the biopsy specimen was that of xanthomatous biliary cirrhosis. There were numerous granulomatous areas in the lobules and periportal areas with occasional giant cells. In a recent review[122] of hepatic lesions in ulcerative colitis and regional enteritis an unusual number of cases of biliary cirrhosis was observed. In a case of biliary cirrhosis[82] high titers of complement fixing antibodies were found to liver and other human tissue antigens. The authors assumed an immunologic disturbance. On the other hand, no gamma globulin was found in the liver in 2 cases of biliary cirrhosis by Cohen *et al.*[23]. In a review of the problem of biliary cirrhosis, Cameron[16] considers hypersensitivity a factor in cholangitic and cholangiolitic cirrhosis, and the prominent collections of lymphocytes of Hanot's hypertrophic cirrhosis "perhaps" an expression of local immunity. If one considers that common infectious processes rarely[127] cause cirrhosis of the liver, one wonders if the many[110] cases of liver cirrhosis of cryptogenetic origin could not be based on a hyperimmune mechanism. This may well be the "other and as yet unidentified mechanism" involved in the pathogenesis of Laennec's cirrhosis, recently discussed by Klatskin[78].

GRANULOMATOUS INFLAMMATION IN THE LIVER. Allergic phenomena of the liver are considered medical rarities[56], perhaps because of the inadequacy of current techniques. Pathological findings suggesting participation of the liver in hypersensitivity phenomena are difficult to evaluate. They include extensive eosinophilic infiltrates[52] in the liver associated with eosinophilic granuloma of the stomach and perhaps granulomas observed in liver biopsies of patients with ulcerative colitis[122]. As mentioned in the introduction, several cases with granulomatous inflammation of the liver recently have come to our attention[57]. Granulomatous inflammation has been observed as a result of local sensitization in the experimental animal[53,54]. Granulomas are frequent in tuberculosis; Rich[115] re-

gards granulomas as an expression of hypersensitivity rather than the effect of the specific agent *per se*. Granulomatous lesions may be an expression of drug hypersensitivity with principal localization in the liver[104,135]. Some of the granulomatous lesions attributed to the so-called foreign body reaction have been found to have a hypersensitivity mechanism[119]. Churg and Strauss[22] have called attention to allergic angiitis at necropsy in patients who died with symptoms of severe asthma. Granulomatous nodules have been found widespread in many organs including the liver. In infiltrative eosinophilia, due presumably to parasites, the liver may[31] have gray-yellowish nodules with heavy eosinophilic infiltration. Fairley[38] described granulomatous lesions in the liver in experimental and human schistosomiasis. Pseudotubercles and giant cells were apparent early in the infection, as was the eosinophilic exudate. The latter was assumed by the author to be provoked by miracidial metabolic activity, while granulomata were thought to derive from mechanical stimulation. Granulomas may be observed though in the liver when mechanical irritation by a schistosomal egg spine is not present, as in granulomas observed in the liver as a result of ascaridic infestation[103]. It has been suggested that the various conditions in which granulomata occur could have a common denominator[41]. Hypersensitivity seems a reasonable assumption of such a common denominator. All observations, nevertheless, concerning the allergic mechanism of granulomatous lesions are based on indirect evidence.

Newer techniques[17,23,109] have been applied recently to the study of the liver and the hypersensitivity phenomena occurring in it. They may prove useful in proving directly the hyperimmune mechanism of the granulomatous inflammation. The fluorescent antibody technique and tagging with radioactive substances may provide promising results in future studies.

COMMENTS. Knowledge of etiology and pathogenesis in many cases of liver disease is incomplete. There has been an increased prevalence of hepatic necroses in necropsy material in recent years[15], the nature of which has been poorly understood. Wätjen[134] assumed an allergic mechanism in centralobular necroses, and based his assumption on the reproducibility of analogous histological changes in experimental animals by immunological techniques. Such necroses are readily observed in sensitized rabbits when the eliciting injection is into the portal stream. In his opinion, the liver plays a central role in hypersensitivity reactions and the central zones of hepatic lobules may be the site of antigen-antibody interaction. This may well be true, but this assumption awaits more direct evidence. The liver seems to play an important role in anaphylactic shock[90-93], most apparent in the dog. The liver appears to be responsive to immunologic stimulation, both when the challenge is directed to other sites in the body, or when directed into the liver substance. Findings in the experimental animal have varied; fatty degeneration has been observed by many[2,13,26,29,44,74,95], vascular engorgement[13,29,44] and cellular infiltration: lymphocytic[29,59,95] plasmacellular[14] and eosinophilic[59,95,126]. Necroses have been frequently observed[4,12,21,36,59,94,114,116] both in the experimental animal and in human material. Hemorrhage[21,27] and vascular thrombosis[4,21,94] have been observed occasionally. Histiocytic proliferation[14,95], granulomata and giant cells[95,126] have been reported rarely. Most of these changes are non-characteristic and there is need for a direct demonstration of the antigen-antibody rela-

tionship. The liver has been found responsive to the Arthus procedure[3,21], to the Shwartzman reaction[1,4,14,50]; and there has been liver involvement in the Auer type of procedure, investigated by Knepper[79]. This last procedure with regard to the liver awaits more extensive studies. Hypersensitivity with localization in the liver has been assumed on clinical bases in a variety of conditions, including serum sickness, food and drug intolerance and asthma. While in conditions following injection of immune serum, shock and liver disease seem related to an allergic event, the evidence is very slight in other conditions. The well-cited case of fish allergy as a cause of liver disease reported by Schmengler[117] is an example in point. With all the suggestive evidence, there is need for more direct proof that the subacute yellow atrophy developed on a hypersensitivity basis. In asthma, the relation of some cases of severe asthma to periarteritis nodosa would suggest allergic involvement of vessels in various organs including the liver; but in a given case, the antigen-antibody interplay in the liver should be proven. The allergic nature of some cases of acute hepatitis has been advocated mainly on the basis of concomitant symptoms known to occur in hypersensitivity states. The liver may be a part of a generalized hypersensitivity reaction after drug administration. Such reactions may be fatal[67], with demonstration of pathological changes in the liver. In such cases the direct demonstration of both antigen, in this case of haptenic nature, and the corresponding antibody would be necessary evidence that the histological findings are really based on an antigen-antibody union. Unfortunately, such evidence has not been obtained in the past.

The use of "autoimmune" is a misnomer even if the evidence is convincing that the liver tissue itself reacts with the corresponding antibody and causes changes. In such cases, isoimmunity is involved with damage caused to other animals of the same species. The concept of auto-immunity should be reserved for pathological states in the diseased animal and with no disease in others of the same species. Serologically, this would mean reactivity of the serum with the patient's own tissue and no reactivity with tissues of other individuals. The complement fixation reaction used by some workers[46,47,83,84,86,132], may be a valuable index of liver disease activity. One should bear in mind that with appropriate technique, Kidd and Friedenwald[75] were able to demonstrate a natural antibody in the blood serum, which reacts *in vitro* with constituents of many normal tissues, including liver. Similarly, Olitzki and Bernkopf[111] observed a high percentage of positive precipitin tests between the sera of patients with infectious hepatitis and cholesterolized alcoholic extracts of ether-treated liver tissue. But a substantial number of normal sera also gave a positive reaction. Conclusions based, therefore, on positive complement fixation tests, or precipitin reactions, valid when appropriate controls have been instituted, need careful wording. The significance of such positive reactions is as yet poorly understood.

The concept that liver cirrhosis may arise on an immunological basis is based on circumstantial evidence only. Very few authors[80,137] have attempted to produce such conditions in the experimental animal and more work with newer methods seems appropriate. Granulomatous inflammation of the liver is not rare. The outcome of such inflammation is unknown. The allergic nature of granulomatous inflammation awaits further demonstration by newer methods.

What are these new methods? First, there is great need for work with purified substances. When one injects a complex antigen such as horse serum, the many components of it take part in the immunological event and the result may be a deceiving simplicity. Hawn and Janeway[65] injected electrophoretically purified albumin into rabbits and obtained findings of interest at regular time intervals. In some animals hepatic lesions were observed, with proliferation of endothelial cells of sinusoids and necrosis of hepatic cells with polymorphonuclear infiltrates. Another important new development involves studies with labeled antigens or labeled antibody. Campbell and Garvey[17] injected an S_{35}-labeled sulfanilic azo-ovalbumin into normal and sensitized rabbits. The antigen was found to persist for many months and in large amounts, particularly in the liver. The importance of such information with regard to liver pathology is obvious. Others[60] injected I_{131} labeled ovalbumin and reached similar conclusions. Nairn *et al.*[109] applied a fluorescent tracer to whole serum or albumin to study lesions in the liver in induced hypertension. These studies have no direct bearing on our subject, but the method may produce important information on antigen-antibody relationships in liver disease. This method has been recently applied to liver disease by Cohen *et al.*[23] and valuable information has been obtained as to the localization of gamma globulin in the liver in postnecrotic cirrhosis, biliary cirrhosis and infectious hepatitis. Hunter *et al.*[71] tagged with fluorescent dyes the serum gamma globulin of patients with liver disease. Liver tissue obtained at biopsy or at necropsy was treated with the tagged protein and binding has been observed in 3 patients. (6)

Summary. The liver plays an important role in anaphylactic shock. Exclusion of the liver from the circulation prevents the effect of the eliciting injection. The liver is responsive to immunologic stimulation, both when the site of application of the stimulus is outside the liver or brought directly into the substance of the liver. The Arthus and the Shwartzman phenomena can be produced in the liver and this organ may participate in the Auer type of procedure. Hypersensitivity phenomena have been assumed to occur in the liver in various ailments such as serum sickness, food allergy, asthma, periarteritis nodosa, but conclusive proof is lacking that an antigen-antibody interaction plays a role in the pathology of the liver. These considerations also are true with regard to infectious hepatitis, hepatic involvement in drug hypersensitivity, and liver cirrhosis. There is no proof of an "autoimmune" mechanism in liver disease. Granulomatous inflammation of the liver awaits conclusive evidence that such granulomata are due to antigen-antibody interplay. Newer methods with purified antigens, with tagged antigens or tagged antibodies should be applied in the study of liver disease of possibly immunological character. (16) (28) (33) (38) (46)

Conclusions. 1. The liver plays an important role in anaphylactic shock. (58)

2. The liver is responsive to antigenic stimulation occurring in the organism.

3. Conclusive, direct evidence, by newer methods, is necessary to support the concept of an antigen-antibody interaction in hepatic disease.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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JUVENILE DELINQUENCY

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ANY discussion of juvenile delinquency today must suffer from at least two disadvantages: first, the term has not been defined with anything close to satisfactory rigor. In the Colorado statutes[16], for example, a delinquent child is defined as one who "violates any criminal law of this state, a single violation shall be sufficient for the court to find the child delinquent; or who is disorderly, immoral or incorrigible; or who is habitually truant from school; or who is beyond the control of his parent, guardian or other lawful custodian to the extent that his welfare or that of others is seriously endangered (no statement about the nature of the control itself, or even about its absence [author's comment]), or who knowingly associates with thieves, vicious or immoral persons; or who is growing up in idleness or crime; or knowingly visits or enters a house of ill repute; or who drinks intoxicating liquors, or who is guilty of rowdyism or disorderly conduct about the public streets, vacant lots, or loiters thereon without being on any lawful business or occupation; or makes indecent proposal or habitually uses vile, obscene, vulgar, profane or indecent language, or is guilty of disorderly or immoral conduct."

This language is similar to that of the first legal definition in the United States, that of Illinois, written in 1889[10].

Although in actual practice this law is generally sensibly interpreted; nonetheless, if taken literally, it would exclude few children from being defined as delinquent.

Secondly, psychiatric definitions do no better. Aichhorn[1] defines Wayward Youth (not necessarily the same as our current term "delinquent") as "not merely delinquent and dissocial children, but also so-called problem children and others suffering from neurotic symptoms." In the introduction to his book he makes the very cogent point that "every child is at first an asocial being. . . ."

Certain others have placed great emphasis on the phenomenon of acting out[17]. Johnson has recently published an excellent discussion[11]. This means that psychological conflicts are translated into gross behavior, either directly or symbolically, with relatively

little generation of anxiety or psychiatric symptom formation. Acting out is not limited to, nor pathognomonic of, juvenile delinquency.

Perhaps the most useful definition, and the one most often applied in fact, is a social one. This would categorize juvenile delinquency as behavior in a child which is chronic, deviant from the average behavior of other children in the same culture, destructive of things or productive of pain in persons, and which arouses sufficient anger or fear in adult witnesses as to cause the creation of strong prohibitions.

In this paper many different terms are used to indicate kinds of abnormal behavior: criminality, psychopathy, and others. None of these is intended to be equated to juvenile delinquency; although for reasons already cited, there may be confusion and overlap.

There are several well-known variables which operate in an illogical way to affect the labeling of a child or a course of behavior as delinquent.

Social class, to use another loose term, is one of these. Certainly parental prestige in the community, and the parents' willingness to use their prestige to cover up the delinquency of a child, is often a most important factor. Such protectiveness may be a disguise for active, although unconscious, encouragement of delinquent behavior.

(A teenage girl was seen by the author, at the request of her parents, for delinquent behavior. The parents believed her guilty of a large number of variegated improper acts. Investigation revealed the very high probability that her only delinquency was leaving home in the night and joy-riding in the family car, a very minor offense in comparison to those of which her parents suspected her. They had been aware of this activity for about two years; but never, during two years, had it occurred to them that they might remove the keys from the ignition lock of the car, or lock the car doors.)

Adelaide Johnson has given us a most useful concept of "super-ego lacunae" to characterize a basis for this kind of parental behavior and the response to it of the child[11]. The delinquent behavior of the child may furnish a vicarious satisfaction to a parent. Unconscious encouragement may be provided, with the help of which the child acts out impulses strongly present in parents, but in them successfully forbidden.

The relative publicity of the delinquent behavior is another matter of importance. Certainly, among many children, illegal things are done which never come to the attention of adults. Any need to confess, or to brag, radically changes the perception of the behavior.

There is a fairly common pattern in a first visit of a group of boys to a house of prostitution. This may happen in the situation of freedom from usual supervision: the trip of an athletic team to a strange city, or the first pass after joining an armed service. Beginning with joking challenges, and at first rationalized as just going to have a look, without patronizing the prostitutes, the enterprise grows until powerful group sanction combines with other factors so that members of the group have intercourse with the prostitutes. Such escapades seldom remain secret, since some of the group have such strong needs to confess, to brag, or both.

The morbidity of this disorder, however defined, is of very great interest. The articles written in today's nonscientific publications are practically endless. Many of them are rather alarmist, and take the position that juvenile delinquency is increasing, both in amount and in the seriousness of the delinquent behavior.

In May, 1957, a report of the U.S.

Senate Subcommittee to Investigate Juvenile Delinquency predicted that, if present rates continue, one million children will appear before courts in 1965.

Attempting to take samples from all around the world[2] there was apparently a very widespread upsurge of juvenile delinquency in the aftermath of World War II. Thereafter, except in England and the United States, almost all police authorities feel the problem was brought back under control.

The "Teddy Boys" of London, organized in relatively permanent delinquent gangs, and the uniformed gangs of New York City have continued, with unabating or even increasing degrees of criminal activity, to be sources of serious concern. Special schools, special counselors, specially assigned police have not been successful in controlling either gang activity, or less organized forms of delinquency.

There is no possibility at this time, perhaps in part because we are dealing with a poorly delineated syndrome, to speak definitively of etiology. One can, however, review the usual classes of etiologic factors, and examine whether or not there may be positive correlations.

Hereditary factors are usually among the first to be considered. "Pseudoheredity," that is learning delinquency within certain family relationships, which are exactly repeated from one generation to another, is a potent source of error. The incidence of *diagnosed* juvenile delinquency is probably higher in depressed socio-economic strata. In these strata there is relatively little social mobility.

There may be a meaningful, although unjustified, contamination of the term juvenile delinquent by the old and now outmoded "constitutional psychopathic inferior." Such contamination would tend to be increased by the great therapeutic difficulties, to be mentioned later.

Such studies, as the not very careful but very well-known ones, describing the Juke family[4] and the Kallikaks[7], are pertinent. More recently, and much more carefully, Rosanoff[15] compared identical twins, and found over 60% of concordance in criminality.

The constitutional school, begun by Lombroso[13] and continued more recently by Kretschmer and his students have hypothesized correlation between physique and various modes of abnormal behavior. The anthropologist, Hooton[9], also supports this hypothesis. It has been severely criticized by the Gleucks[6] among others.

The evidence then, in this area, must be considered inadequate, thus far, to support a correlation between any physical characteristic and delinquency.

Healy and Bonner[8] and Cervantes[3] have been much impressed by the increased incidence of juvenile delinquency in abnormal families: broken homes, missing parents, socially deviant parents, cultural maladjustment, and the like.

I have been impressed, in the delinquent children I have seen, by two factors. First, these children often acquire, by means of delinquent behavior, something of value to them, which is not available by any other means. Ritualized security and affection are available in the delinquent gang, becoming particularly important, when they are not to be found within the family or any other grouping. A kind of "love" is found in premature or promiscuous sexuality. Things, even food, may sometimes be had only if stolen. The highly symbolic automobile may be available to a teenager only in that form of theft called "joy-riding."

Secondly, much delinquent activity has as its objective the mastery of fear and anxiety[5], and not at all the alleged

objective. Hence, the great importance of the "dare." Delinquent children who drink excessively often say that they dislike the taste of what they drink, and also dislike the experience of being drunk. They often drink large amounts of unpleasant beverages, in the presence of peers, to prove their courage.

The same thing is true of sex. These children frequently confess to having no sexual pleasure from their extensive activities, and are more often led to them by being dared, than by being courted or seduced.

Attempts to treat this syndrome, in the case of the individual patient, or to control the social consequences, in the case of groups, have been of several kinds.

Social agencies, primarily Family and Children's Services and Welfare Services, have very widely undertaken to treat delinquency by case work methods strongly influenced by child guidance methods. Usually, in addition to the child's being seen by a case worker, one or both parents are also seen. Sometimes psychiatric consultation is used. Partly because of large case loads, and partly because of limitations of this kind of technique, there is usually a selection process through which only the more mildly delinquent children are kept in treatment.

Some cities, such as New York, have established special schools for delinquents. These have not been long in operation, but the possibility exists that they are prohibitively difficult for teachers, and produce little change in delinquent patterns. They do, however, keep the children in school longer. Early discontinuation of school is very common among delinquents. This is, in my opinion, effect rather than cause.

Social workers, and some young religious leaders have managed successfully to introduce themselves into delinquent groups and to be accepted by them. They witness, without expressing moral judgments, the delinquent behavior. They refrain from participation. Very slowly and delicately, they attempt to reduce the delinquent behavior by interpreting its unreality. Redl[14] has pointed out that these children are highly skilled in testing an incomplete social reality. To be "dumb," "square," "snowed," or to "sucker in" are causes in them for great chagrin and damage to self esteem.

There are several special communities for delinquent boys, a prototype in this country being Father Flanigan's Boystown. In general, these institutions bring about improvement in a majority of their boys. The institutions cannot handle serious problems, however, and are few in number.

Most child psychiatric clinics undertake treatment of mild delinquency. In more serious cases, with impulsiveness and serious acting out, it is generally held that intramural treatment, with the imposition of physical inhibition of the acting out, is needed. We have, across the United States, almost no facilities for the inpatient care of delinquent children.

A word should be said about Juvenile Courts. These courts, almost always having at least small numbers of psychiatrists, psychologists and social workers on their staffs, use a combination of treatment and punishment or threat of punishment. They have been ingenious in the development of supportive adjuncts, such as associations of socialized men and women who are willing to spend time with a delinquent child, at least offering him a normal model which he can use if he will and can. Again, courts have good results with mild cases, but the more severe ones, sooner or later, are usually treated by penal quarantine.

Summary. Relatively recently there

has been created, betwixt crime and sickness, the diagnostic category of delinquency.

Juvenile delinquency is an antisocial behavior pattern, variously diagnosed and treated according to geography, class, race, and the like. The etiology of the disorder is not well known, but is probably a multiple one, having among the variables a disordered family in which the child cannot satisfy certain emotional needs. For most cases, several kinds of fairly successful treatment are available. For severe cases, there is usually no treatment available.

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BOOK REVIEWS AND NOTICES

THE LIPIDS. VOL. I: CHEMISTRY; VOL. II: BIOCHEMISTRY; VOL. III. BIOCHEMISTRY. By HARRY J. DEUEL, JR., Dean, Graduate School and Professor of Biochemistry, University of Southern California, Los Angeles. Pp. 982, 919 and 1065; illustrated. New York: Interscience Publishers, Inc., 1951, 1955 and 1957. Price, $21.00, $25.00, and $25.00 respectively.

IN this monumental treatise, Dr. Deuel undertook the task of correlating the available information regarding the various components included under the general classification of lipids. What was projected as a two volume work actually required three, the last being published after the author's untimely death in 1956.

Volume I is devoted to the Chemistry of Lipids. After a section on the General Characteristics and Classification of Lipids, there follows a systematic review of the chemistry of fatty acids, glycerol, neutral fats, waxes, higher alcohols including sterols, triterpenes, glyceryl ethers, colored fats, hydrocarbons, phosphatides, cerebrosides, carotenoids and related compounds. Other chapters deal with the distribution, properties, and chemistry of Vitamins A, D, E, and K.

Volume II is concerned with the Digestion, Absorption, Transport, and Storage of Lipids. Successively, there is summarized the accumulated knowledge regarding the digestion and absorption of fats in the gastrointestinal tract, the digestibility of fats and of lipids other than fats, the blood lipids, the occurrence of lipids in the animal as a whole, and lipid distribution in specific tissues and their secretions.

Volume III deals with the Biosynthesis, Oxidation, Metabolism, and Nutritional Value of Lipids. After a general transitional discussion of lipid digestion, absorption, transport, and storage, there is a specific consideration of the biosynthesis, oxidation and metabolism of triglycerides, phospholipids, and fatty acids in the animal body. In other chapters, the question of the conversion of fat to carbohydrate is discussed, followed by a critical review of the intermediary metabolism of various lipids, including cholesterol. Next, the metabolism and nutritional value of the Vitamins A, D, E, and K are considered. Finally, the physiology and biochemistry of the essential fatty acids and the nutritional value of fats are discussed.

The author and subject indices to the 3 volumes are helpfully complete.

This reviewer marvels at the scope, thoroughness, and lucidity of these volumes. It is all the more remarkable as the product of a single author. In Dr. Deuel's own words, "In this day of specialization, when many texts are compilations of sections prepared by masters in the several fields discussed, one may question the advisability of the preparation by a single author of a monograph on a wide field such as the chemistry of lipids. An author attempting such a task can obviously not be an authority in all fields. Therefore, a book of this nature must necessarily be less involved and more understandable to readers who, also, are not specialists in the individual fields. The style should be more uniform and the book as a whole more cohesive when prepared by a single writer." The author successfully achieved all of his goals in the preparation of this treatise.

Everyone concerned with lipids and their metabolism, whether as biochemist, clinical investigator, nutritionist, or clinician will do well to consult these volumes which will long serve as a reference standard for the field. C Z.

FERMENTE, HORMONE, VITAMINE UND DIE BEZIEHUNGEN DIESER WIRKSTOFFE ZU EINANDER. VOL. 1, FERMENTE. Edited by ROBERT AMMON AND WILHELM DIRSCHERL. 3rd ed. Pp. 564; 34 ills. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $23.00.

THE available material on enzymes has grown during the last decades to astronomical figures. The need for a summarizing textbook in this field justifies the third edition of this 3-volume handbook. The present first volume on enzymes will soon be followed by one on hormones and one on vitamins. The authors are both outstanding workers in enzymology. They have solved, in a most satisfactory way, the problem of summarizing and of sifting critically the extensive work in enzymology. The chapter presenting an introduction to enzymology, written by R. Ammon, is a masterpiece. It is a guide to the understanding and the study of enzymes, to the understanding of their kinetics, and to the practical application of this knowledge to biological

problems. Both authors deserve the thanks of all who need information in enzymology. A translation of this book into the English language would seem highly desirable.

B.K.

THE CENTRAL NERVOUS SYSTEM AND BEHAVIOR. Selected Translations from the Russian Medical Literature. Prepared and Distributed by the RUSSIAN SCIENTIFIC TRANSLATION PROGRAM, NATIONAL INSTITUTES OF HEALTH, Bethesda, Maryland. Pp. 1051. Washington: U.S. Department of Health, Education, and Welfare, Public Health Service, 1959.

THIS volume is a collection of 70 articles translated from the Soviet medical literature. It was prepared primarily for the use of the participants at the Third Macy Conference on the Central Nervous System and Behavior. They were selected as being generally representative of some of the more recent Soviet research concerned with the understanding of human behavior. Many of the articles are not normally available to those who do not read Russian. The Department of Health, Education and Welfare is, therefore, to be complimented for making these articles available in translation form not only to the Conference above noted but to medical and scientific libraries to which copies are being distributed.

R.K.

THE PLACENTA AND FETAL MEMBRANES. EDITED BY CLAUDE A. VILLEE, PH.D. Pp. 404; 87 ills. Baltimore: The Williams & Wilkins Co., 1960. Price, $10.00.

"THE Placenta and Fetal Membranes" contains not only the proceedings of a conference on the placenta but a series of review articles on various aspects of placental function, a review of the present literature and a list of current investigations related to the placenta and its activities. The participants include clinicians as well as basic scientists all of whom are active in the study of some phase of placental physiology.

The review articles include discussions of various phases of placental function such as hormone production, circulation, transmission of antibodies between mother and infant, support of the fetus in utero and of various histophysical, biochemical and pathologic aspects, a bibliography of more than 2700 articles related to the placenta and its function which were published between 1946 and 1958 is appended. These are listed under various broad catagories (anatomy, physiology, and others) and further subdivided into more specific groups. Brief descriptions of all the known current investigations with the investigators also are listed.

The subject material of the conference itself was rather broad, including discussions of anatomy, blood flow, hormonal production, placental transfer and some aspects of fetal function.

This volume should be interesting to investigators in the general field of reproduction but particularly important to those concentrating on placental, uterine and fetal physiology. There is little to attract the practicing physician.

J.W.

PSYCHIATRY: DESCRIPTIVE AND DYNAMIC. BY JACKSON A. SMITH, M.D., Clinical Director, Illinois State Psychiatric Institute, Chicago, Illinois. Pp. 342. Baltimore: The Williams & Wilkins Co., 1960. Price, $7.50.

As the title states, this book presents a bird's eye view of descriptive and dynamic psychiatry. Within the covers of this book is to be found a survey of the history of psychiatry, schools of psychiatry, psycho-dynamics, psychiatric examinations, a description of the more usual psychiatric entities including child psychiatry, and a section on emotional problems in the geriatric patient. A bibliography and index is included.

The book is written clearly with great conciseness. The more experienced psychiatrist may not find interest in the book because it is too superficial. People less experienced in psychiatry may find the book lacking in descriptive detail. The great value of the book is in its presentation of a few most pertinent facts about each subject discussed.

M.B.

ANATOMY: REGIONAL AND APPLIED. BY R. J. LAST, M.B., B.S. (ADEL.), F.R.C.S., Professor of Applied Anatomy, Royal College of Surgeons of England. 2nd ed. Pp. 741; 372 ills., many in color. Boston: Little, Brown & Company, 1959. Price, $15.00.

IN these days when the time allotted to anatomy in the medical curriculum has been severely curtailed and when specialty boards require candidates to pass examinations in basic sciences, the old encyclopedic texts are being replaced by those taking a more streamlined approach. This book addresses itself particularly to those who know some anatomy already but who wish to review or to widen their understanding. All regions of the body

are covered and in many places the author has enlivened his descriptions with pertinent bits of developmental or comparative anatomy and has also helpfully suggested a few new ways of interpreting anatomical facts (example, knee and larynx).

The book does not employ the new nomenclature and this, together with its loose organization, would be a handicap to a beginning student.

All anatomists are grateful for the bibliography giving the original papers which have put certain proper names into our vocabulary.

R.H.

TRIFLUOPERAZINE, FURTHER CLINICAL AND LABORATORY STUDIES. Pp. 191; 3 ills. Philadelphia: Lea & Febiger, 1959. Price, $3.50.

THIS brief monograph about one of the many phenothiazine compounds is comprised of 21 original reports. Eight reports deal with the use of trifluoperazine in the treatment of mental and emotional disorders in outpatients, five with its use as adjuvant therapy in psychosomatic conditions, two with its use in mentally defective children, and three with its use as an antiemetic drug. Only one report is devoted to its pharmacology, and two are concerned with laboratory studies in trifluoperazine-treated patients. The final report deals with the extrapyramidal symptoms which occur in trifluoperazine-treated patients.

R.S.

KINDERHEILKUNDE. By PROF. DR. MED. ERWIN GRUNDLER AND DR. MED. GERHARD SEIGE. Pp. 846. Stuttgart: Hippocrates-Verlag, 1960. Price, DM 29.

THIS is a pocket-size compendium of General Pediatrics intended for the student and busy practitioner familiar with German. It is divided into an introductory section containing information on normal growth and development, techniques of infant feeding, and immunization; a brief review of the clinical features of all the important pediatric diseases, including some rare ailments; and a final 100-page formulary which is quite up-to-date and complete.

The book will interest only those English-speaking readers who desire to learn about standard pediatric methods used in Europe, if not to use them. A typical case in point is the recommended treatment of pyloric stenosis by "conservative" measures, surgery to be resorted to if these fail.

The book lists normal serum electrolyte values in milligrams per cent and gives no information about basic parenteral fluid therapy, the latter usually considered to be somewhat more important than the "normal" size of the sella turcica, tabulated on page 39.

W.E.

CLARK'S APPLIED PHARMACOLOGY. By ANDREW WILSON, M.D., PH.D., Professor of Pharmacology and General Therapeutics, University of Liverpool, and H. O. SCHILD, M.D., PH.D., D.SC., Reader in Pharmacology at the University of London, University College, London. 9th ed. Pp. 750; 165 ills. Boston: Little, Brown and Company, 1959. Price, $10.00.

THE ninth edition brings this well known and well written textbook reasonably up-to-date. It continues to live up to its title and main purpose of providing a scientific basis for the study of therapeutics. The book is organized principally according to the systems of the body with one or more chapters devoted to each system. The first two chapters deal with general principles. In addition, one chapter is devoted to products of protein breakdown and immune reactions, one to vitamins, 6 chapters to the pharmacology of infectious diseases, one to disinfectants, and one to the pharmacology of the skin. Two new chapters have been added on psychopharmacology, one devoted to methods. The treatment of the subject matter is brief and practical.

R.S.

METABOLIC ASPECTS OF RENAL FUNCTION. By WILLIAM D. LOTSPEICH, M.D., Professor and Chairman, Department of Physiology, University of Cincinnati College of Medicine. Pp. 214; 58 ills. Springfield, Ill.: Charles C Thomas, 1959. Price, $7.50.

THE three areas which appear to be most active and pressing in renal physiology are: (1) the general problem of water and osmoregulation, (2) the regulation of renal blood flow, and (3) the biochemical aspects of renal function. It is with the last of these that the author deals in this book, the main theme being the relation between cell metabolism and the specialized functions that characterize the kidney. He has brought together and placed in a larger context much of the research with which he has been concerned in the past 15 years, particularly in the areas of phosphate and amino acid transport, ammonia excretion, the mechanism of action of phlorizin, the relation between renal excretion and utilization of metabolic substrate, and the role of the tricar-

boxylic acid cycle in the kidney. He adds a chapter on organic acids and bases, though he has not worked in this field, because of its "fascinating trail of research, full of frustrations and brilliant strides," and because "it has never been brought together before in its consecutive development."

The writing is lucid and supplemented by excellent illustrations and diagrams. There is included some speculation by the author, as would be expected in a book of this type, and ideas for experimentation are suggested here and there. Students of renal physiology will find the material of great interest and the literature review of particular value.

T.D.

THE FLUIDS OF PARENTERAL BODY CAVITIES. By PAUL D. HOEPRICH, M.D., AND JOHN R. WARD, M.D., University of Utah College of Medicine. Pp. 98; 11 ills. New York: Grune & Stratton, Inc., 1959. Price, $4.75.

THESE authors have filled a vacuum in the available literature concerning body fluids. They present techniques of collection, methods of examination and criteria for interpretation with regard to serous fluid from the pleural, pericardial and peritoneal surfaces, to synovial fluid and cerebrospinal fluid. They have included as well, brief but well considered sections on the anatomy of the secreting surfaces, and the physiology and biochemistry of the normal and pathological secretory states. Altogether, this volume presents material almost impossible for each of us to collect for ourselves. It should be available to every clinical pathologist and practicing physician.

J.B.

TEXTBOOK OF OTOLARYNGOLOGY. By DAVID D. DEWEESE, M.D., Clinical Professor of Otolaryngology, University of Oregon Medical School, and WILLIAM H. SAUNDERS, M.D., Associate Professor of Otolaryngology, Ohio State University College of Medicine. Pp. 464; 354 ills. St. Louis: C. V. Mosby Company, 1960. Price, $8.75.

THIS textbook, designed primarily for the medical student and general practitioner, presents a clear, systematic digest of current knowledge in the field of otolaryngology. Although the opening chapter on physical diagnosis considers the methods of examination and standard techniques in considerable detail, the discussions of anatomy and physiology in the following chapters are confined to the data essential for orientation. In the noncontroversial approach to diagnosis and treatment, there is constant emphasis on practical aspects. The inclusion of chapters on lesions of the oral cavity, speech disorders, dizziness and vertigo, the salivary glands and cysts and tumors of the neck provides unusually broad coverage of the field. Profusely illustrated with fine reproductions of photographs, roentgenograms and line drawings, with a bibliography in the form of selected readings appended to each chapter, and with a well organized and concise text, this volume offers a maximum of readily accessible information. It deserves the highest recommendation.

H.S.

A GENETIC FIELD THEORY OF EGO FORMATION. By RENE A. SPITZ, M.D., University of Colorado, Denver. Pp. 123; 4 ills. New York: International Universities Press, Inc., 1959. Price, $3.00.

BASED on direct observation of infants, Spitz draws parallels between embiological and psychological concept formation. The author emphasizes the earliest stages of affective development. At every level of the infant's evolution there exists a varying proportionality between the role of maturation and that of development in the different sectors of infant personality.

This book includes references, a brief biography of Dr. Spitz and a list of his publications.

M.B.

HISTOLOGIE UND MIKROSKOPISCHE ANATOMIE DES MENSCHEN. By PROF. DR. WOLFGANG BARGMANN, Kiel. 3rd ed. Pp. 820; 658 ills., some in color. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $16.55.

HISTOLOGY is presented in this textbook in a dynamic fashion, microscopic anatomy being traced to submicroscopic structures, and both being integrated with physiological, biochemical and pathological observations. The text is well written and lucid. The illustrations are of high didactic value. Each chapter is furnished with an excellent selection of references. Details cannot be discussed here, but it is noteworthy that this is one of the rare texts where the reticuloendothelial system is defined accurately, and the endocrine tissues are described in full. Previous editions of this book have been praised here and abroad as a masterpiece of a leading histologist and excellent teacher. The present edition has been substantially enriched by additions especially to the chap-

ters on general histology through incorporation of recent physical and chemical techniques. The book is highly recommended to experts as well as students in medicine and biology. W.E.

EINRICHTUNG UND METHODE DES KLINISCHEN LABORATORIUMS. BY PROF. DR. MED. E. GOETZE, University of Jena. Pp. 246; 69 ills. Jena: Gustav Fischer, 1959. Price, $5.20.

THIS book contains a concise description of the apparatus and techniques in biochemistry and clinical microscopy used in modern hospitals. Toxicology, microbiology or histology are not considered. The book is well written. The text is authoritative and up-to-date. Many references pertain to the American literature. The book should be useful especially to students in medicine and technology if they read German. W.E.

NEBENSCHILDDRÜSENINSUFFIZIENZ UND TETANISCHES SYNDROM. BY PROF. DR. J. QUANDT AND DOZ. DR. MED. W. PONSOLD. Pp. 176; 38 ills. Jena: Gustav Fischer Verlag, 1959. Price, DM 17,80.

THIS is an authoritative study by a neuropsychiatrist and a pharmacologist of the tetanic syndrome and of parathyroid insufficiency. The tetanic syndrome is discussed by Quandt. It is described as a neuropathological syndrome characterized by hyperirritability of the central nervous system, especially of its subcortical regions, by a low threshhold of neuromuscular excitability, and by increased sensitivity to hypokapnia. The syndrome may be caused by disturbances in mineral metabolism (parathyroid insufficiency), by functional or organic changes of the cortical areas which suppress the subcortical regions involved in this disorder, or by activation of these regions, by psychic or somatic stimuli (neurogenic tetany), or by alkalosis due to hypokapnia (respiratory tetany, gastric tetany). Parathyroid insufficiency is discussed by Ponsold. It is described as a disturbance in mineral metabolism. This may be due primarily to injury of the glands (surgery, hemorrhage, toxic-infectious damage, unknown causes), or it may be secondary to excessive demands upon parathormone secretion (poisoning with calcium precipitating chemicals, nutritional calcium deficiency, vitamin D deficiency, steatorrhea, kation exchange therapy, renal disease and others). In the last chapter Quandt discusses the normocalcemic tetanic syndrome in relation to psychic experiences and neuroses. The book contains excellent descriptions of the history of tetany, of the anatomy and histology of the parathyroids, the biochemistry and physiology of parathormone, and various clinical aspects of the syndrome. Also it is furnished with good illustrations and an adequate list of references including many in English. The book is highly recommended to those who are interested in tetany and hypocalcemia. W.E.

BIOLOGY OF THE PLEUROPNEUMONIALIKE ORGANISMS. BY D. G. EDWARD AND 79 OTHERS. Edited by J. B. NELSON. (Ann. New York Acad. Sci., **79**, Art. 10, pp. 305-758.) Pp. 453; illustrated. New York: New York Acad. Sci., 1960. Price, $5.00.

IN this monograph many papers are presented that take in a wide variety of investigations on pleuropneumonialike organisms (PPLO). Some of the papers are on morphology, classification, isolation and propagation of PPLO. There are also excellent discussions on physiology and serological relationships of PPLO, as well as the effect of chemotherapeutic agents. Of particular interest are the areas concerned with human and animal pathology. L-forms of bacteria are also discussed as well as the possible relationships between L-forms and PPLO.

This is an excellent monograph and those intersted in PPLO will find it highly informative and a valuable reference book which covers areas of interest to workers in both the medical and veterinary sciences. R.S.

PATHOLOGY OF THE HEART. Edited by S. E. GOULD, M.D., D.Sc., Professor of Pathology, Wayne State University College of Medicine. 2nd ed. Pp. 1138; 621 ills., some in color. Springfield, Ill.: Charles C Thomas, 1960. Price, $32.50.

SEVEN years have elapsed since the publication of the first edition of this outstanding volume. Extensive revisions and additions have been made, necessitating a complete resetting of type. Five new chapters have been added: The Conduction System, by Maurice Lev, Lesions of the Aorta, by Ira Gore, Cardiopulmonary Disease, by Averill A. Liebow, Surgery of the Heart, by Charles P. Bailey and J. E. Imbriglia, and Histochemical Procedures in the Study of Heart Disease, by J. F. A. McManus and M. A. Guerrero. The other chapters are by the same authors as in the first edition.

Once again the editor and contributors

are to be congratulated on a job extremely well done. The reviewer has found the volume to be one of the most valuable on his library shelves and highly recommends it to cardiologists, internists and pathologists. In the rapidly expanding field of cardiology it provides a unified consideration of basic knowledge and research potential which should be well nigh indispensable for anyone working in this field. T.D.

SIXIÈME CONGRÈS INTERNATIONAL DE LA MÉDECINE D'ASSURANCES SUR LA VIE. By 39 AUTHORS. Pp. 397; 53 ills. Paris: Masson & Cie, 1959. Price, 40 NF.

THIS volume is a series of articles reported in either French, English, German or Italian on various aspects of life insurance medicine. The sole contribution from the United States is an excellent paper on prognosis following nephrectomy by Henry B. Kirkland, M.D., Chief Medical Director of the Prudential Insurance Company of America. The other authors are various European physicians. Three articles on tuberculosis attest to the improved mortality of recent years. There is a good group of papers on infectious hepatitis. A section on the Prevention of Aging is concerned on one hand with Social Security and on the other with possibilities for the prevention of atherosclerosis. This volume would be of interest principally to physicians engaged in the practice of life insurance medicine. P.L.

HISTOCHEMISTRY: THEORETICAL AND APPLIED. By A. G. EVERSON PEARSE, M.A., M.D., M.R.C.P., D.C.P., Reader in Histochemistry in the University of London. 2nd ed. Pp. 998; 245 ills. and 10 color plates. Boston: Little, Brown and Company, 1960. Price, $20.00.

THIS is the second edition of a most excellent book first published in 1953. The work gives a complete coverage of the important and rapidly expanding field of histochemistry. The book is generally divided into two sections.

The first section deals with tissue preparation, fixation, freeze drying and substitution, and basic and critical discussions of histochemical methods for proteins and amino-acids, nucleic acids, carbohydrates, lipids and lipid complexes, aldehydes and ketones, and enzyme histochemistry. Included are chapters on immunohistochemistry, pigments, inorganic constituents, fluorescence microscopy, autoradiography, and electron histochemistry. Some of these are necessarily brief, but the sections on enzyme histochemistry, lipids, and carbohydrates are outstanding for completeness, clarity of discussion, and critical appraisal of the inherent limitations of the available methods. In fact it is just this critical approach, mostly based on personal experience, that makes this section valuable. Careful explanations of mechanisms of reaction are also presented.

The second section is a compendium of the histochemical methods discussed in the text, and by itself would be a valuable textbook. Arranged as an appendix, this section presents, chapter by chapter, the detailed techniques of histochemistry. A valuable addition to the second edition is a molecular weight and purchase source of over 500 compounds discussed in the text.

This book is a complete guide to the novice as well as the practicing histochemist and is most highly recommended. H.W.

THE ALKALOIDS: CHEMISTRY AND PHYSIOLOGY, VOL. VI. Edited by R. H. F. MANSKE. Pp. 442; 2 ills. New York and London: Academic Press, Inc., 1960. Price, $14.00.

THIS volume is a continuation of the series of reviews begun by Manske and Holmes in 1950. The motivation for the publication of additional volumes is expressed by the editor in the following statement taken from the Preface: "Since the appearance of Volume V, many syntheses bordering on the spectacular, have been achieved; new and hitherto unsuspected structures have been revealed; a surprisingly large number of new alkaloids have been discovered; many structural problems have been solved; and the biogenetic pathways have been formulated, explored, and proved." Thus, Volume VI has been prepared as a supplement to Volumes I and II. Contributions have been made by the following authors: K. Mothes, alkaloids in the plant; Leo Marion, the pyrrolidine and pyridine alkaloids; Nelson J. Leonard, Senecio alkaloids; G. Fodor, the tropane alkaloids; J. B. Hendrickson, the strychnos alkaloids; Gilbert Stork, the morphine alkaloids; W. C. Wildman, colchicine and related compounds and alkaloids of the amaryllidaceae.

The desire of the editor to present a review of more recent advances has been achieved insofar as it is practically possible in a published work. The assignment of many chapters to new authors has provided the opportunity for frankness in the discussion of previous

omissions and has permitted a fresh approach to some subjects. Yet the integration of this chapter with previous documentation has been well done without undue repetition. The literature of the past ten years has been exhaustively reviewed with some additions from earlier publications. Difficult points of chemistry and particularly steric relationships are illustrated by the liberal use of conformational formulae which have been excellently reproduced. The judicious use of tables has relieved much of the boredom which would attend recounting of data respecting a compound or series of compounds.

If any criticism is to be voiced, it is probably in the comparatively small attention given by some of the authors to physiological data. On the other hand, the chemical reviews are outstanding and make the volume one of the most valuable of the series.

J.S.

DAS ANTIKÖRPERMANGELSYNDROM. Edited by S. BARANDUN, H. COTTIER, A. HÄSSIG, AND G. RIVA. Pp. 539; illustrated. Basel: Benno Schwabe & Co, 1959 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, Sfrs. 38 ($8.00).

THIS book consists of reprints of ten papers by 2 authors published during 1959 in volume 26 of the Helvetica Medica Acta. Five of these papers deal with the role of humoral antibodies in infection, the recovery and testing of γ globulin preparations, and the measurement, the chemistry and the maturation of immune globulins. Three papers (filling about half the book) are devoted to the clinical manifests of the antibody deficiency syndrome, while the remaining 2 papers deal with the pathological anatomy of this condition, and with the therapy of bacterial infections with γ globulin preparations. The clinical papers are based on 232 cases from the world literature and 41 cases of their own. All papers are authoritative and comprehensive. Each paper is furnished with an extensive list of the pertinent literature and with an English and French summary. Details cannot be discussed here, but it should be noted that the antibody deficiency syndrome is not identical with agammaglobulinemia. It is true that most cases showed marked reduction or absence of the gammaglobulins, but some cases revealed normal or increased values. The latter consisted either of normal nonspecific or abnormal pathological gamma globulins (paraproteins). The beta globulins, on the other hand, were almost always absent. All cases were characterized by a marked decrease or complete absence of humoral antibodies. The clinical and morphological manifestations of the syndrome were quite heterogeneous. Congenital forms of agammaglobulinemia with or without lymphopenia can be distinguished from acquired forms and from normo-gammaglobulinemic forms. Also primary or idiopathic forms can be distinguished from secondary or symptomatic forms due to myeloma, macroglobulinemia of Waldenstroem and others. This excellent book is highly recommended to all students and physicians interested in plasma proteins, antibodies, white blood cells or infection.

W.E.

CANCER OF THE CERVIX: DIAGNOSIS OF EARLY FORMS. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P. AND MAEVE O'CONNOR, B.A. Pp. 114; 22 ills. Boston: Little, Brown and Company, 1959. Price, $2.50.

THE fourth Ciba Foundation Conference was devoted to a discussion of the earliest phases of Cancer of the Cervix and the proceedings are published in this volume. The participants were experienced clinicians and pathologists, all of whom are active in the study and treatment of genital tract malignacy. Four of the seven papers are devoted to the microscopic changes with carcinoma-in-situ of the cervix, one to clinical detection of the lesion and one to the relationship between beta glucuronidase and cervical carcinoma. The seventh paper concerns atypical endometrial hyperplasia. Much of the discussion which is recorded verbatim revolved around the problems of establishing exact criteria for invasion.

Most of the papers will be of more interest to pathologists than to practicing gynecologists, but anyone who treats cervical cancer can gain much useful and helpful information from a study of this small volume.

J.W.

GESTATION: TRANSACTIONS OF THE FIFTH CONFERENCE, MARCH 11, 12 AND 13, 1958. Edited by CLAUDE A. VILLEE, PH.D., Assistant Professor of Biological Chemistry, Harvard Medical School. Pp. 262; 114 ills. New York: The Josiah Macy, Jr. Foundation, 1960. Price, $5.75.

THE fifth Macy Conference on Gestation was devoted primarily to discussions of the biology and circulation of the placenta and to prolonged gestation in cattle which are reported in this volume. Some of the ma-

terial presented during the previous conferences is reconsidered in the light of recent knowledge and new material has been added. Presentations and discussions are reported verbatim.

The structure and function of placentas of submammalian species is discussed in great detail. A considerable portion of the conference was devoted to the circulation through the placental vessels and the intervillous spaces. It was suggested in one presentation that the site of placental implantation was an important factor in the development of pregnancy toxemia; the condition being far more common when the implantation site was in the fundus than in the lower segment. A study of prolonged pregnancy in cattle indicated that length of gestation was in part controlled by genetic factors.

This material holds little interest for practicing physicians but should prove helpful to those particularly interested in the details of placental structure and function. J.W.

PHYSICAL PHARMACY. By ALFRED N. MARTIN, PH.D., Professor of Physical Pharmacy, Purdue University. Pp. 692; 168 ills. Philadelphia: Lea & Febiger, 1960. Price, $15.00.

PHYSICAL PHARMACY covers the field of pharmacy from a scientific approach. The properties of pharmaceutical systems and fundamentals underlying the formulation, compounding and stabilization of medicinal products are very well evaluated and expounded. The correlation of physical chemistry to physical pharmacy has been done in a concise systematic way.

The introduction of this book as a Physical Pharmacy textbook to the upper classes of pharmacy students is, however, premature. It precludes an advanced knowledge of mathematics, graph and chart interpretation, and especially of calculus. There is a need of more explanation of the theoretical material and of the problems presented.

In its present form it serves as a good reference book for undergraduate students or as a textbook for graduate students.

C.M.
R.S.

NEURO-ROENTGENDIAGNOSTIK DES SCHAEDELS. BY PROF. DR. MED. H. DIETRICH, Munich. 2nd ed. Pp. 289; 385 ills. Jena: Gustav Fischer Verlag, 1959. Price, DM 49.

DESPITE the fact that most radiology textbooks cover pathology of the skull, this monograph uniquely represents a comprehensive approach to the roentgenographic examination of the skull. Great demand for the first edition exhausted the supply rapidly and for this reason this new revised edition has been recently published by the well known expert in this field.

The first chapter reviews the techniques of the examination of the skull with all special views. Chapters on the normal and abnormal development of the skull follow. They are quite valuable at this time of extensive study of retarded children; the data on dysostosis in childhood have been enhanced during recent years by the numerous articles that have appeared in the American literature. In the third chapter diseases of the skull due to metabolic or hormonal disorder, reticulosis, tumors and infectious diseases are described. This is followed by the description of fractures and their healing process, as well as postoperative defects and foreign bodies. The fourth and last chapter describes skull changes due to intracranial diseases. Pressure signs of intracranial tumors in various locations are here primarily discussed. Finally, there is a review of all possible intracranial calcifications.

. A 13-page extensive international bibliography is enclosed. The 385 illustrations have been well reproduced and are very instructive.

This book is a valuable addition to the existing good books on pneumoencephalography and arteriography concerning the primary and secondary changes of the skull. Most any branch of medicine, namely, neurology, otolaryngology, pediatrics, internal medicine or surgery shall be delighted to have this book and make use of it. W.B.

SURGERY IN WOBLD WAR II. NEUROSURGERY, VOLUME 2. Editor-in-Chief, COLONEL JOHN BOYD COATES, JR., MC, USA, Editors for Neurosurgery, R. GLENN SPURLING, M.D., BARNES WOODHALL, M.D.; Associate Editor, ELIZABETH M. MCFETRIDGE, M.A. Pp. 705; 283 ills. and 12 color plates. Washington, D.C.: United States Government Printing Office, 1959. Price, $7.00.

THIS second and final volume of the neurosurgical history of World War II is concerned with injuries to the spinal cord and peripheral nerves and includes a chapter on lesions of the intervertebral disc. The authors believe that the most dramatic achievement of the entire neurosurgical program of World

War II was the advance made in the management of paraplegics.

Part I on injuries of the spinal cord includes historical and administrative notes, the management of acute compound cord injuries, urological aspects, the management of paraplegic patients in the zone of interior hospitals and the treatment of ruptured intervertebral discs.

Part II on peripheral nerve injuries includes historical notes, standard methods of examination of peripheral nerve injuries, anatomic approaches to the more commonly injured nerves, techniques of peripheral nerve repairs, bone and nerve injuries, peripheral nerve injuries complicated by skin and soft tissue defects, peripheral neurovascular injuries, causalgia following combat incurred injuries of the peripheral nerves, peripheral nerve grafts, neuropathologic changes in battle incurred injuries of the peripheral nerve, physical therapy in the management of nerve lesions and orthopedic techniques for use in irreparable nerve injuries.

The Appendices include routine procedures for the care of transverse myelitis cases, statistical data on battle wounds and battle injuries of the spinal cord, vertebra, and peripheral nerves.

This volume is fascinating reading and it is a tribute to the neurosurgeons, neurologists, nurses, and technicians, most of them anonymous, who gave their utmost for the medical care, comfort and rehabilitation of the wounded soldier.

It should be required reading for residents in the specialties of neurosurgery, neurology, urology, general surgery, orthopedics, and rehabilitation. It is also a reference work for specialists in these fields.

Aside from its scientific value, the volume will prove interesting and stimulating reading to medical students and to those interested in the historical aspects of World War II. M.S.

SHAPES OF SANITY. By AINSLIE MEARES, M.D., B. AGR. SC., D.P.M. Pp. 468; 191 ills. Springfield, Ill.: Charles C Thomas, 1960. Price, not given.

THIS work deals with the use of modelling in psychiatry. The author, seeking shorter methods of psychotherapy, employs modelling as a psychodynamic agent and refers to the treatment as plastotherapy. Combined with hypnosis (hypnoplasty) these techniques, in the hand of the author, have significantly shortened the time of psychotherapy.

The author discusses the technique and theoretical aspects of plastotherapy. There is a chapter on the psychodynamics of this treatment and modelling as an aid in diagnosis. Part II of the book deals with hypnoplasty.

The illustrations are excellent. The book is well written and will appeal to workers in the field. M.B.

THE TRIUMPH OF SURGERY. By JÜRGEN THORWALD. Translated by RICHARD AND CLARA WINSTON. (Original German title: *Das Weltreich der Chirurgen*, Steingrüben Verlag, Stuttgart, West Germany, 1957.) Pp. 454; 58 ills. New York: Pantheon Books, Inc., 1960. Price, $6.50.

THIS highly readable book, which takes up the history of surgery where Jürgen Thorwald's previous volume "The Century of the Surgeon" left off, permits the reader to experience vicariously surgery's greatest triumphs. Through its pages one can follow surgical history in the making by its brilliant and courageous pioneers.

In his earlier book, Mr. Thorwald told the story of surgeons in the latter half of the 19th century who, as a result of discoveries in anesthesia, antisepsis and asepsis, made surgery a modern discipline. Now, the fictitious Dr. Hartmann again becomes an eyewitness to describe great moments in surgical progress during the past eighty years. He begins at the Third International Medical Congress at London in 1881 to renew his narrative. At this time a new era was dawning in surgery as technical achievements extended operative approaches to the brain, spinal cord and peripheral nerves, eye, ear, thorax, abdominal viscera, gynecologic and urologic disorders.

Dr. Hartmann meets great medical men from many nations in this era: Theodor Kocher, Swiss pioneer of modern goiter surgery; William Macewen, Scottish neurosurgeon; Marion Sims, American gynecologist; Morell Mackenzie, English otolaryngologist who attended the unfortunate German Emperor Frederick III; Jean Martin Charcot, eminent French neurologist; Sigmund Freud, Austrian experimentor with local anesthesia; The Mayo Brothers, John B. Murphy, William Halsted, William Welch and numerous others.

"The Triumph of Surgery," like "The Century of the Surgeon," provides a fascinating on-the-spot account of surgical advances. The book is nicely illustrated and has an index. One must read this beautifully written volume, and its predecessor, to fully appreciate their accuracy and appeal. F.R.

TECHNIQUE ET PRATIQUE DE LA CORRECTION PROTHÉTIQUE DES SURDITÉS. By JACQUES DEHAUSSY, D. PHARM., Faculté de Medicine et Pharmacie de Lille. Pp. 266; 75 ills. Paris: Masson et Cie, 1959. Price, NF 30,00.

THIS monograph contains comprehensive but concise information concerning every aspect of audiometry. There is an evaluation and comparison of all types of audiometers and hearing aids in current use and directions for the construction and use of sound conditioned test chambers. Every subjective and objective test for hearing is discussed with emphasis on the practical applications while the significance of tuning fork tests is evaluated in the light of audiometric findings. Many difficult subjects such as the mathematics related to the physics of sound are presented with exceptional lucidity. Full discussions are given of the peep show and psychogalvanic techniques in the examination of children as well as the variation in methods employed from earliest infancy to senescence. Much valuable information is included concerning discrimination tests. In the selection of hearing aids for adults and the subsequent psychologic guidance, there is constant emphasis on practical applications. The illustrations amplify the text and there is a complete bibliography. This work can be highly recommended to all audiologists and otologists.

H.S.

YOUR HEART: A HANDBOOK FOR LAYMEN. By H. M. MARVIN, M.D., Associate Clinical Professor of Medicine, Yale University School of Medicine. Pp. 335. Garden City, New York: Doubleday & Company, Inc., 1960. Price, $4.50.

UNCOOPERATIVENESS of a patient commonly means lack of understanding produced all too frequently by failure of communication between physician and patient. Willingness to follow a physician's advice is a trait, not a commodity, and must be created and bred, and cannot be bought or ordered. Yet, it is not difficult to obtain and has as its reward the fulfillment of a physician's goal to restore a healthful and useful life. Dr. Marvin demonstrates in this book why he is a master clinician. In reading it, you have the feeling that you are the patient and he is your physician, explaining what you have and discussing what is known about it, supporting his statements by direct quotes from the recent literature. There is neither dogmatism nor prejudice, especially in controversial matters presently unsettled. But this is not a book that is only factual and consequently cold; rather, it is warm and gentle like the author's personality, and provides our patient a better understanding of what is wrong and what we are trying to do about it, not only now for him but also for the future for all mankind. Although it is written primarily for laymen, physicians will profit too.

J.Z.

CLINICAL DISORDERS OF HYDRATION AND ACID-BASE EQUILIBRIUM. By LOUIS G. WELT, M.D., Professor of Medicine, University of North Carolina. 2nd ed. Pp. 336; 11 ills. Boston & Toronto: Little, Brown & Co., 1959. Price, $7.00.

THE first edition of Dr. Welt's book published in 1955 was an unqualified success, and justifiably so since it presented a difficult, but immensely important subject with a clarity of expression possible only to one thoroughly versed in his subject and blessed with superb teaching talent. The present edition adds the significant advances that have been made in this field in the interval, plus a chapter by Dr. Robert W. Winters dealing with the special problems presented by the pediatric patient. The bibliography has increased from 437 to 766 references, and represents the cream of the literature on this subject. There are few physicians, be they general practitioners, internists or surgeons, who would not profit greatly by a careful study of this book.

T.D.

EARLY DIAGNOSIS. Edited by HENRY MILLER, M.D., F.R.C.P., Physician in Neurology, Royal Victoria Infirmary, Newcastle upon Tyne. Pp. 400. Baltimore: The Williams & Wilkins Co., 1959. Price, $6.50.

THIS book is written specifically for the general practitioner, although there is much in it that could be of value to many specialists. Twenty-five outstanding English physicians have contributed to the ensemble, including such as Ian Aird, Lord Cohen of Birkenhead, and John McMichael, to name but a few. It is very refreshing to the reviewer to find a book written from the viewpoint of the diagnostic problem as seen *in the home* of the patient. The men who have written it have evidently had experience other than that of the Ivory Tower. There is a wide range of topics including The Acute Abdomen, The Acute Specific Fevers, Fits and Faints, Alcoholism, Poisoning, Common Occupational Diseases, and many others. This is very basic medicine, full of common sense and practical knowledge. It is to be hoped that it will be

as widely read in the United States as it will certainly be in England. T.D.

CHRISTOPHER'S TEXTBOOK OF SURGERY. Edited by LOYAL DAVIS, M.D., Chairman, Department of Surgery. Northwestern University Medical School. 7th ed. Pp. 1551; 1597 ills. Philadelphia: W. B. Saunders Company, 1960. Price, $17.00.

THE seventh edition of this well-known textbook was written by a distinguished group of surgeons, representing various parts of the United States and Canada. The surgical material is presented clearly and, in most instances, includes the physiopathology of the particular area discussed. It is the reviewer's feeling that this type of presentation is vital if the book is to be used by third and fourth year medical students. Too often, a multiple-authorship book consists of a group of papers by distinguished surgeons and is not written with the medical student in mind. In a book of this size, one can always find sections where the method of presentation could be improved in the opinion of the reviewer. Once again in the seventh edition as in previous editions, there is no adequate mention made of the value of the liver function studies in differential diagnosis of surgical and non-surgical diseases of the liver and the biliary system. From the student's point of view, this could be corrected.

One can summarize the seventh edition by stating that it is an excellent book which has obviously been written by men of competence with experience in teaching. It can be recommended highly for use by third and fourth year medical students, and it is also an excellent reference manual for interns, residents and those in the surgical teaching field. The subject of surgery obviously cannot be completely covered by any single volume. This book is equally as good as any textbook of surgery now published and superior to many. H.C.

CARDIAC AUSCULTATION, INCLUDING AUDIO-VISUAL PRINCIPLES. By J. SCOTT BUTTERWORTH, M.D., Associate Professor of Medicine, M. R. CHASSIN, M.D., Associate Professor of Clinical Medicine, R. MCGRATH, M.D., Associate Professor of Clinical Medicine, and E. H. REPPERT, M.D., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School. 2nd ed. Pp. 102; 68 ills. New York & London: Grune & Stratton, Inc., 1960. Price, $6.25.

RECENT advances in machine techniques of cardiac examination, plus the requirement for accuracy in diagnosis demanded by the spectacular development of cardiac surgery, have resulted in a renewed interest in, and understanding of cardiac auscultation. The physician of today finds that a mastery of auscultatory techniques, applicable at the bedside, is vastly rewarding. Unfortunately, all too often, idolatry of the machine results in serious neglect of this field of knowledge.

Dr. Butterworth and his associates have had extensive experience in the teaching of auscultatory techniques and they have produced what the reviewer considers to be the most concise, accurate text on this subject, and one that is supplemented by extremely well chosen illustrations to make understanding easy. It is a book that can be read in a relatively short period of time, and the correlation with principles of pathophysiology makes the learning process far easier than would be the case if it were necessary to memorize a host of apparently unrelated facts. The bibliography is brief, but the reader, if sufficiently stimulated (as it is to be hoped he will be) can move on to a more exhaustive text such as that of McKusick. T.D.

CLINICAL ENDOCRINOLOGY. I. Edited by EDWIN B. ASTWOOD, M.D., Professor of Medicine, Tufts University, Boston. Pp 724; 171 ills. New York and London: Grune & Stratton, Inc., 1960. Price, $18.75.

GALDSTON has said, "The long view of the history of science reveals the pattern of periodic diversifications in interest and knowledge, that is, of specialization, followed by periods wherein the synthetic unification of knowledge is achieved. Science is never more innately consonant and rewarding than during its unitary stages." Endocrinology today is illustrative of a trend toward a unitary stage. No specialist can afford to be unaware of the hormonal influences regulating the organ or organs with which he has to deal any more than he can neglect the prevading influence of the central nervous system. The volume reviewed should be welcomed not only by endocrinologists, but by general practitioners, internists, and specialists of all types.

Ten years ago Grune & Stratton published Progress in Clinical Endocrinology under the editorship of Dr. Samuel Soskin. This was a very valuable and popular volume. The present work was at first to be a second edition, but as the book took shape it was evident that it was not a revision but one that should stand as an entirely new and far more extensive volume. The editor has had the assistance of 81 authors, each of whom is outstanding in his own field. Included are such

as Barrter, Denton, Ingle, Jacobson, Nordin, Page, Pincus, Ricketts, Sprague, and Venning, to mention but a few out of an illustrious group. Whether the reader wishes to know the latest relative to aldosterone, or osteoporosis, or glucagon, or the hormone therapy of cancer, or a host of other subjects he can do no better than to make use of this book. The reviewer can discover only one omission which he considers important, that of the Lipid Mobilizing Hormone. It is to be sincerely hoped that, with the continued advance of endocrinology, Volumes II, III and IV will become available as needed. T.D.

FUNDAMENTALS OF CHILD PSYCHIATRY. By STUART M. FINCH, M.D., Associate Professor of Psychiatry and Director of the Children's Psychiatric Hospital, University of Michigan School of Medicine. Pp. 334. New York: W. W. Norton and Company, Inc., 1960. Price, $5.95.

DR. FINCH discusses the usual, psychoneurotic and psychotic disorders of childhood. Included is a chapter on parental psychopathology, and the principles of child psychotherapy. References, a reading list and index enhance the value of the book.

This book is written for doctors, social workers and psychologists. It is written in a clear, concise style, and is essentially descriptive in nature. The case illustrations are lucid and interesting. In good pedagogic style, Dr. Finch offers a summary after each psychiatric entity he describes. M.B.

X-RAY TECHNOLOGY. By CHARLES A. JACOBI, B.Sc., R.T. (A.R.X.T.), M.T., (A.S.C.P.), AND DONALD E. HAGEN, R.T. (A.R.X.T.), Oregon Technical Institute. 2nd ed. Pp. 453; 320 ills. St. Louis: C. V. Mosby Co., 1960. Price, $10.00.

GREATLY improved over the first edition, this is a valuable book for the technician-in-training in the field of radiography and a useful text to be followed in the formal teaching of this subject. It embraces an intelligent condensation of the broad fields of physics, anatomy and physiology, and it stresses the important subject of correct positioning in radiography. Especially valuable are the large number of illustrations from Merrill which clarify the descriptive text regarding positioning by showing the part in correct position with respect to Roentgen-ray tube and film together with a reproduction of the radiograph so obtained. G.B.

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